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Clinical Diagnosis of Lipid Disorders

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Atherosclerotic cardiovascular disease is a major health problem in the United States. In particular, coronary heart disease (CHD) is the leading cause of death in men and women in the United States, as well as in other industrialized countries. Extensive observational epidemiologic data within and between populations have strongly linked such various factors as untreated hypertension, diabetes, cigarette smoking, and lipid abnormalities to the development of CHD. With respect to lipoprotein parameters, elevated total and low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) have been strongly associated with CHD risk. Emerging evidence suggests that other lipoprotein abnormalities also are associated with premature CHD, including elevated levels of lipoprotein(a), triglyceride-rich lipoproteins such as small very-low-density lipoproteins and intermediate-density lipoproteins, small and dense LDL particles, and the magnitude of postprandial lipemia. Extensive primary and secondary clinical trial evidence has established that favorably altering dyslipidemias through diet and a variety of pharmacologic agents produces clear improvements in CHD end points. The extent of this benefit depends on the presence or absence of clinical atherosclerotic disease, as well as other CHD risk factors, and the severity of one or more lipoprotein abnormalities. CHD patients and individuals with multiple risk factors, but free of clinical CHD, derive the greatest absolute benefit from lipid treatment directed at reducing LDL-C. The dyslipidemias that impart high risk are severely elevated LDL-C (> 200 mg/dL), combined high LDL-C and low HDL-C (< 35 mg/dL), and combined hyperlipidemias (non-HDL-C > 200 mg/dL with low HDL). The purpose of this review is to aid the primary care physician in identifying these important dyslipidemias and to critically analyze the relative importance of various lipoproteins on atherosclerotic risk.

CLINICAL ASSESSMENT OF DYSLIPIDEMIAS IN ADULTS

Complete clinical guidelines for the detection, evaluation, and treatment of dyslipidemias in adults have been published by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) II. These guidelines algorithmically stratify coronary heart disease (CHD) risk assessment and

treatment by whether or not CHD or other atherosclerotic vascular disease is clinically present (primary versus secondary prevention). Patients considered at highest risk for future cardiovascular events are those with known CHD or other vascular disease. The focus of the ATP II guidelines is on the control of low-density lipoprotein cholesterol (LDL-C), although high-density

lipoprotein cholesterol (HDL-C) and triglycerides also impact risk-management decisions.

CLINICAL EVALUATION IN PRIMARY PREVENTION

For patients without known clinical cardiovascular disease, the initial clinical assessment includes a complete history, a physical examination, and basic laboratory testing to determine the baseline lipoprotein profile. All adults older than age 20 should

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have total cholesterol and HDL-C measured at least every 5 years. Both of these measurements can be made on a nonfasting sample. Finger-stick blood techniques can be used for this lipid screening; however, sampling of venous blood in a fasting state is required for decision-making concerning intervention. The history should include efforts to detect symptoms that may be suggestive of undiagnosed vascular disease, such as chest pain and claudication. Detailed questioning about lifestyle is mandatory and should include assessment of dietary habits, weight gain, exercise patterns, alcohol

consumption, and cigarette smoking. Family history data should address whether parents and/or their first-degree relatives as well as siblings have known vascular disease, lipid abnormalities, or such other CHD risk factors as hypertension, diabetes, or obesity. The physical examination should include blood pressure, height and weight (including calculated body mass index), and inspection for manifestations of dyslipidemia (xanthelasma, tendinous or tuberous xanthomas, arcus cornealis) and vascular disease (bruits and peripheral pulses). If the lipid profile is abnormal, additional laboratory testing should include fasting glucose, thyroid and liver function tests, and a urinalysis to detect possible secondary causes of dyslipidemias. A resting electrocardiogram may be warranted in men older than age 45 and postmenopausal women.

CHD risk assessment in primary prevention should include classification based on total cholesterol (**Table I**) and determination of risk factors, as defined by the NCEP ATP II (**Table II**). For patients with desirable total cholesterol and HDL-C levels and fewer than two risk factors, reevaluation of lipid levels is recommended in 5 years, though patients should be counseled on the health benefits of low-fat diets, exercise, maintaining a reasonable body weight, and avoiding tobacco use. Patients with a borderline-high total cholesterol, HDL-C ≥ 35 mg/dL, and fewer than two risk factors should have their lipid values repeated in 1 to 2 years, as well as receive counseling on achieving and maintaining a healthy lifestyle. Dietary advice for these patients should be to restrict total calories and total saturated fat, which is the basis of the Step I diet (**Table III**).

TABLE I. NCEP CLASSIFICATION OF CHD RISK BASED ON TOTAL CHOLESTEROL

<i>Classification</i>	<i>Total Cholesterol (mg/dL)</i>
Desirable	< 200
Borderline-high	200-239
High	≥ 240

NCEP = National Cholesterol Education Program; CHD = coronary heart disease. Data from the National Cholesterol Education Program (Adult Treatment Panel II). *JAMA*. 1993;269:3015-3023.

TABLE II. CHD RISK FACTORS IN THE NCEP ATP II ALGORITHM

<i>Factor</i>	<i>Scenario</i>
Positive	
<input type="checkbox"/> Age	Male ≥ 45 years Female ≥ 55 years, or premature menopause without HRT
<input type="checkbox"/> Family history of premature CHD	Definite MI in first-degree relatives Male ≤ 55 years or female ≤ 65 years
<input type="checkbox"/> Current cigarette smoking	
<input type="checkbox"/> Hypertension	BP $\geq 140/90$ mm Hg or taking antihypertensive medications
<input type="checkbox"/> HDL-C	< 35 mg/dL (on several determinations)
<input type="checkbox"/> Diabetes mellitus	
Negative	
<input type="checkbox"/> HDL-C	≥ 60 mg/dL (for primary prevention, subtract one risk factor)

CHD = coronary heart disease; NCEP = National Cholesterol Education Program; HRT = hormone replacement therapy; MI = myocardial infarction; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol. Data from the National Cholesterol Education Program (Adult Treatment Panel II). *JAMA*. 1993;269:3015-3023.

TABLE III. STEP I DIETARY RECOMMENDATIONS

<i>Nutrient</i>	<i>Recommended Intake</i>
Total fat (% of total calories*)	≤ 30
Saturated fat	8-10
Polyunsaturated fat	≤ 10
Monounsaturated fat	≤ 15
Carbohydrates (% of total calories)	≥ 55
Protein (% of total calories)	15-20
Cholesterol (mg/d)	< 300

*Total calories = calories sufficient to achieve a reasonable body weight. Data from the National Cholesterol Education Program (Adult Treatment Panel II). *JAMA*. 1993;269:3015-3023.

All patients with a high total cholesterol, low HDL-C, or borderline-high total cholesterol with two or more risk factors should undergo a complete fasting lipoprotein profile. Because the determination of LDL-C requires measurement of triglyceride, the venous blood sample should be obtained while fasting, usually after 12 hours. The LDL-C

is not measured directly but is estimated using the Friedewald formula:

$$\text{LDL-C (mg/dL)} = \text{Total cholesterol} - \text{HDL} - (\text{triglyceride} \times 0.2).$$

This calculation is not valid if the fasting triglyceride level is > 400 mg/dL and/or the patient has type III hyperlipidemia (elevated intermediate-

density lipoproteins [IDL]). In these circumstances, the LDL-C can be determined by ultracentrifugation in a specialized laboratory.

Diagnostic lipid determinations should be deferred for at least 2 weeks following any minor illness and for at least 8 weeks following any major illness or surgery because total cholesterol, LDL-C, and HDL-C can decline by as much as 30% under these conditions. In pregnant women, total cholesterol and LDL-C can be physiologically increased; therefore, it is advisable to avoid lipid testing until 6 months after delivery. Before any clinical decisions are made regarding risk or treatment, at least two fasting lipid profiles should be obtained 2 to 4 weeks apart.

LDL-C is considered desirable at < 130 mg/dL, borderline high at 130 to 159 mg/dL, and high risk at ≥ 160 mg/dL. Elevated risk status in primary prevention, according to the NCEP ATP II, includes: (1) LDL-C 190 to 219 mg/dL in young men (< 35 years of age) and premenopausal women; (2) LDL-C 160 to 189 mg/dL and fewer than two risk factors; and (3) LDL-C 130 to 159 mg/dL with two or more risk factors. Recommendations for the Step I diet, exercise, and weight loss (if needed) are mandatory for these individuals, with appropriate follow-up lipid determinations over a period of 3 to 6 months. The goal of lifestyle intervention is a reduction of the LDL-C below 190, 160, and 130 mg/dL, respectively, for the above-mentioned risk categories. For elevated-risk patients, the ultimate goal of this approach is to retard atherogenesis so as to prevent CHD events later in life. Pharmacologic intervention may be indicated for the highest risk primary prevention individuals, whose LDL-C remains above the following cut-points despite lifestyle changes: (1) LDL-C ≥ 220 mg/dL in young men and premenopausal women; (2) LDL-C ≥ 190 mg/dL and fewer than two risk factors; and (3) LDL-C ≥ 160 mg/dL with two or more risk factors. Drug treatment to lower LDL-C is discussed in another article appearing in this publication.

The focus on LDL-C in defining risk and targeting treatment efforts is supported by the results of primary prevention studies in men and women in whom LDL-C was significantly reduced.

Although low levels of HDL-C strongly predict CHD risk, clinical trial evidence that increasing HDL impacts future CHD events is not as convincing as are the data for LDL. The ATP II classifies low HDL-C as one risk factor that can increase the need to lower LDL-C with diet and drugs.

Epidemiologic data, such as from the Framingham Heart Study, have shown that the risk of CHD is substantially higher if the total cholesterol to HDL (TC/HDL) ratio is > 5 and the LDL to HDL (LDL/HDL) ratio is > 3 . However, the ATP II did not focus on these ratios because they do not provide information as to which individual component — LDL-C or HDL-C — requires modification. Clearly, substantial reductions in LDL-C will reduce the TC/HDL and LDL/HDL ratios.

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The ATP II also recognized that a high level of HDL-C (≥ 60 mg/dL) has been associated with lower risk of CHD in epidemiologic studies. These experts recommended that such a high HDL level could negate one positive risk factor, so that a clinically borderline risk-intervention situation (eg, primary prevention, two CHD risk factors, and LDL 160 to 189 mg/dL) may not require therapy beyond lifestyle change. Note that in the presence of three or more risk factors, a high HDL-C level is not considered sufficiently protective, and the case should be considered high risk. This situation illustrates how a high HDL could result in a TC/HDL ratio < 5 and lead the physician to not consider the patient high risk.

CLINICAL EVALUATION IN SECONDARY PREVENTION

All patients with known CHD (which includes

previous coronary artery bypass grafting, angioplasty, or angiographic evidence of significant coronary atherosclerosis) or clinical atherosclerotic disease of the aorta, carotid arteries, or lower-extremity arteries are at high risk for acute coronary events in the near future. A full fasting lipoprotein profile is required for all these patients. Total cholesterol, LDL-C, and HDL-C concentrations are lower than usual during the recovery phase after a myocardial infarction, after an episode of unstable angina, and following coronary artery bypass grafting. Therefore, lipoprotein measurements obtained more than 24 hours following one of these events will result in levels that may not truly reflect the patient's background exposure to abnormal lipoprotein particles. A lipid profile obtained within the first 12 hours should be more representative and can be used for therapeutic decisions. If it is not done during that time period, it should be deferred for at least 6 weeks.

The ATP II recommends that LDL-C levels ≥ 130 mg/dL be treated with lifestyle intervention and, at the discretion of the physician, with medication. The goal of treatment is an LDL ≤ 100 mg/dL. As several of the clinical CHD end-point trials have demonstrated clinical benefit within 6 to 12 months of initiating drug therapy to lower LDL-C, the practitioner should not hesitate to move to drugs early for secondary prevention. The physician should always conduct a thorough history (focused on lifestyle habits, family history, and lipid profiles of family members), a physical

examination (to detect xanthomas or the presence of otherwise unknown peripheral vascular disease), and pertinent laboratory tests to rule out other causes of dyslipidemias in all secondary prevention patients.

CLASSIFICATION OF DYSLIPIDEMIAS

The Fredrickson and Lees phenotypic classification system (**Table IV**) is not an etiologic classification and does not differentiate between primary and secondary dyslipidemias. However, it can be useful to characterize a patient's lipid disorder. In most instances, the standard lipoprotein profile will be sufficient to determine the phenotype. When

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both total cholesterol and triglycerides are elevated (cholesterol > 240 to < 500 mg/dL and triglyceride > 200 to < 1000 mg/dL), the phenotypic assessment is more difficult. The patient could be type II-b (LDL + very-low-density lipoprotein [VLDL]) or type III (IDL). Although the type II-b pattern is clinically more common than type III, the two

TABLE IV. FREDRICKSON AND LEES CLASSIFICATION OF DYSLIPIDEMIAS

Phenotype	Lipoprotein Elevated	Total Cholesterol	Triglyceride	CHD Risk
I	Chylomicron	NI-↑	↑↑↑↑	Low
II-a	LDL	↑-↑↑	NI	High
II-b	LDL, VLDL	↑-↑↑	↑-↑↑	High
III	IDL	↑-↑↑	↑-↑↑	High
IV	VLDL	NI-↑	↑-↑↑↑	Low
V	VLDL + Chylomicrons	↑-↑↑	↑↑↑↑	Low

CHD = coronary heart disease; NI = normal; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein; IDL = intermediate-density lipoprotein.

disorders can be distinguished by a lipoprotein electrophoresis, which is probably the only situation in which an electrophoresis is clinically indicated. The electrophoresis produces two separate bands for LDL and VLDL and a single broad band for elevated IDL.

As one can see by the classification system, only types II-a and II-b have elevated levels of LDL-C; types I, III, IV, and V are the result of triglyceride-rich lipoprotein elevations. In most of these latter situations, HDL-C is very low and is usually inversely related to triglyceride levels. Most laboratories will not attempt to measure HDL-C if triglycerides are > 500 mg/dL because the method used to isolate HDL from serum (by precipitation of other lipoproteins) is not reliable. If a laboratory does report an HDL under this circumstance, it will most likely be higher than the "true" HDL-C concentration. When one sees marked hypertriglyceridemia in association with an elevated total cholesterol (in an approximately 10:1 triglyceride-to-cholesterol ratio), the phenotype is most likely type V, due to elevated VLDL and chylomicrons. The elevated chylomicrons can be easily detected by storing serum in the refrigerator overnight and observing a floating milky white layer (chylomicrons) over a cloudy supernatant (VLDL).

Another rather simple classification method for dyslipidemias is to organize them into three categories: (1) hypercholesterolemia, due primarily to elevated LDL-C; (2) combined or mixed hyper-

lipidemia, due mostly to increased LDL-C and VLDL, with or without low HDL-C (in rare instances this can be due to increased IDL [dysbetalipoproteinemia]); and (3) hypertriglyceridemia, due to elevated VLDL and/or chylomicrons, as well as their remnants. This classification is most useful for discerning the principal lipoprotein abnormality so as to direct pharmacologic therapy, and it is easier to remember than the phenotypic system. Of course, these classifications can be combined (Table V).

PRIMARY AND SECONDARY CAUSES OF DYSLIPIDEMIA

Most cases of dyslipidemia are multifactorial in origin. Various genetic (primary) disorders impart a predisposition to dyslipidemias; the chief exam-

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ples are listed in Table VI. The conditions most likely to be encountered in a primary care practice are primary moderate hypercholesterolemia (preva-

TABLE V.

INTEGRATED CLASSIFICATION SYSTEM FOR DYSLIPIDEMIAS

<i>Classification</i>	<i>Lipoprotein Involved</i>	<i>Phenotype</i>
Hypercholesterolemia	↑ LDL	II-a
Combined (mixed) hyperlipidemia	↑ LDL, ↑ VLDL, ± ↓ HDL ↑ IDL	II-b III
Hypertriglyceridemia	↑ VLDL	IV
	↑ VLDL, ↑ Chylomicrons	V
	↑ Chylomicrons	I

LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein.

TABLE VI. SELECTED PRIMARY DYSLIPIDEMIAS

<i>Classification</i>	<i>Phenotype</i>	<i>Lipoprotein Involved</i>	<i>Genetic Transmission</i>
Hypercholesterolemia Heterozygous familial	II-a	↑↑ LDL	Autosomal dominant; LDL receptor deficiency
Homozygous FH	II-a	↑↑↑ LDL	Autosomal dominant; total LDL receptor deficiency
Primary moderate	II-a	↑-↑↑ LDL	Unknown; has dominant features
Familial defective Apo B	II-a	↑-↑↑ LDL	Autosomal dominant; apo B mutation
Combined hyperlipidemia Familial combined	II-a, II-b, IV	↑-↑↑ LDL, ↑-↑↑ VLDL	Probably dominant; defect not known but may involve apo B overproduction
Dysbetalipoproteinemia (E-III/E-II)	III	↑ IDL	Unknown but involves apo E-linked metabolic defect
Hypertriglyceridemia Familial	IV V	↑ VLDL ↑ VLDL and ↑ Chylomicrons	Autosomal dominant; Autosomal dominant; metabolic defect not known
Familial chylomicronemia	I	↑ Chylomicrons	Autosomal recessive; apo C-II deficiency or LPL deficiency
Isolated low HDL	NA	↓ HDL	Unknown but may be dominant; metabolic defect not known

LDL = low-density lipoprotein; FH = familial hypercholesterolemia; VLDL = very-low-density lipoprotein; IDL = intermediate-density lipoprotein; LPL = lipoprotein lipase; NA = not available; HDL = high-density lipoprotein.

lence 1/30), familial combined hyperlipidemia (prevalence ~ 1/100), familial hypertriglyceridemia (prevalence ~ 1/200 to 300), and heterozygous familial hypercholesterolemia (FH) (prevalence 1/500). Depending on the lipoprotein defect, physical manifestations include xanthelasmas, premature arcus cornealis, and tendinous xanthomas (marked LDL elevations as in heterozygous FH); eruptive xanthomas and lipemia retinalis (marked triglyceride elevations); and tuberous and palmar xanthomas (IDL elevations). If a primary dyslipidemia is suspected, it is imperative to determine the lipid levels of all first-degree relatives and children. Most of the primary dyslipidemias can be detected before age 20. The treatment of most of these primary lipid disorders will frequently require consultation with a lipid specialist.

The most common secondary cause of dyslipidemia is related to lifestyle: excessive total and

saturated fat intake, which is frequently associated with obesity. Other common secondary causes are diabetes mellitus, nephrotic syndrome, hypothyroidism, chronic renal failure, and several drugs (Table VII). Low HDL-C will be seen with disorders that result in hypertriglyceridemia (particularly diabetes, nephrotic syndrome, and chronic renal failure). In addition, androgens, androgenic progestins (such as norethindrone), and nonselective β -blockers can lower HDL-C levels.

Since atherosclerotic disease occurs more often and at an earlier age in diabetics than in nondiabetics, it is important to recognize the significance of dyslipidemias in diabetes and the need to treat them accordingly. The most common lipid abnormalities are increased serum triglyceride and decreased HDL-C levels. LDL-C may not be elevated, but there is a greater tendency for LDL compositional changes resulting in small, dense

TABLE VII.

SECONDARY CAUSES OF DYSLIPIDEMIA

Hypercholesterolemia

Nephrotic syndrome
 Hypothyroidism
 Obstructive liver disease (primary biliary cirrhosis)
 Pregnancy
 Dysglobulinemias
 Anorexia
 Pharmacologic agents (oral contraceptives, cyclosporin A, isotretinoin)

Hypertriglyceridemia

Diabetes mellitus
 Nephrotic syndrome
 Chronic renal failure
 Hypothyroidism
 Pregnancy
 Dysglobulinemias
 Pharmacologic agents (alcohol, corticosteroids, estrogen, β -blockers, isotretinoin)

particles. These smaller, denser LDL particles are more susceptible to oxidation and have greater atherogenic potential. The cause of hypertriglyceridemia in type 2 diabetics is most likely related to a combination of hepatic overproduction and reduced catabolism by lipoprotein lipase. It has been suggested that insulin resistance enhances these defects, and the so-called insulin resistance syndrome (syndrome X) consists of elevated triglycerides, low HDL-C, hyperinsulinemia, hyperglycemia, and hypertension. Improving insulin resistance will result in an improvement in triglyceride levels and a return of LDL composition to a larger, more buoyant particle. Nephrotic syndrome can be associated with severe elevations in LDL-C, which are roughly correlated with the severity of proteinuria. Many diabetic patients have a combined dyslipidemia resulting from an associated nephrotic state due to nephropathy.

Individuals with hypothyroidism will have elevations in total cholesterol and LDL-C, which can be lowered significantly by supplemental thyroid replacement. A thyroid-stimulating hormone level should be obtained on all patients with significantly increased LDL-C before considering pharmacologic therapy. The possibility that drugs may cause a dyslipidemia should always be considered; when feasible, the physician should consider discontinuing the suspected medication to assess the response. Oral estrogen, in particular,

can significantly increase triglyceride levels in women with baseline hypertriglyceridemia; cutaneous estrogen administration does not, and it is therefore the preferred treatment option for hormone replacement therapy in this situation.

HYPERTRIGLYCERIDEMIA AND CHD RISK

Serum triglyceride levels have been positively associated with CHD risk in univariate analyses of prospective epidemiologic data; however, this association weakens substantially when multivariate analysis is used. In particular, HDL-C, total

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cholesterol, and obesity are some of the analytes that weaken the relationship. The difficulty in establishing a definitive relationship between serum triglyceride levels and CHD risk involves

several factors. First, triglyceride levels are quite variable from day to day, with fluctuations as great as 50% of the baseline. In comparison, total cholesterol and HDL-C levels vary less than 5% from day to day. This variability makes it difficult to establish a reliable long-term association between baseline and follow-up values and subsequent CHD events. Second, triglyceride-rich lipoprotein (TGRL) particles are heterogeneous. Large, cholesterol-poor VLDL particles appear to be less atherogenic than smaller, cholesterol-rich VLDL and IDL particles. Chylomicrons are probably not atherogenic although their remnants may be. A single triglyceride level is not specific enough to tell the physician whether or not atherogenic TGRL particles are present. Third, altered triglyceride metabolism, which results in fasting hypertriglyceridemia, can also produce significant increases in postprandial lipemia. The degree of postprandial lipemia may be a better discriminator of CHD risk than the fasting triglyceride level. Fourth, impaired triglyceride metabolism can produce small, dense LDL particles. It is the total amount of such LDL particles produced in any hypertriglyceridemic patient rather than the magnitude of his or her triglyceride level that probably dictates future CHD risk. Other potentially atherogenic conditions are frequently associated with hypertriglyceridemia, including low HDL-C, the insulin resistance syndrome, and coagulation disorders (eg, increased plasminogen activator inhibitor-1, which inhibits fibrinolysis).

The ATP II defines four categories of fasting triglyceride levels: normal, < 200 mg/dL; borderline, 200 to 400 mg/dL; high, 400 to 1000 mg/dL; and very high, > 1000 mg/dL. A 12-hour fast is necessary to adequately assess triglyceride, and because of variability, at least two to three determinations should be obtained to assess the average baseline. The physician should always consider secondary causes such as diet, obesity, excessive alcohol, oral estrogens in women, and poorly controlled type 2 diabetes. Elimination or control of these causes can reduce triglyceride levels. In the absence of such secondary factors, most high to very high triglyceride levels are primary in nature (types IV and V). For patients with persistent very

high triglycerides, pharmacologic treatment is imperative to reduce the risk for acute pancreatitis. Borderline-to-high triglyceride levels may be associated with an increased risk for CHD if several factors are present: associated total cholesterol elevation (non-HDL-C > 200 mg/dL), low HDL-C, and/or diabetes mellitus. Thus far, no clinical trials have been designed to specifically reduce CHD risk by lowering serum triglycerides.

OTHER LIPID RISK FACTORS

A number of clinical studies have focused on the strong correlation between certain apolipoprotein concentrations and the incidence and severity of CHD. Apoprotein B (apo B), the only protein component of the LDL particle, is the apoprotein with the strongest positive correlation with the incidence and severity of coronary atherosclerosis. It can be elevated even when LDL-C values are "normal," indicating an increased number of small and dense LDL particles. This can be seen in the primary disorder termed hyperbetalipoproteinemia,

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which is probably one of the manifestations of familial combined hyperlipidemia. Measurement of apo B may be useful for risk assessment and may assist in the decision of whether to use drug treatment to further lower LDL-C (and apo B) in certain high-risk primary prevention patients with LDL-C < 160 mg/dL and in CHD patients with LDL-C < 130 mg/dL. Apoprotein A-I (apo A-I), the major protein in HDL particles, has just as strong a negative association with CHD incidence and severity. However, most observational epide-

miologic studies do not suggest that apo A-I concentration is superior to HDL-C concentration in predicting CHD risk. Therefore, it is not recommended that apo A-I be measured for the purpose of defining risk or as an indication of treatment benefit. Although these apolipoproteins can be commercially analyzed, there is no standardization of normal ranges and no consensus on predictive or treatment value. Further study is needed to determine the usefulness of apoprotein measurements as an adjunct to risk evaluation by the routine lipoprotein profile.

Lipoprotein(a) (Lp[a]) is a genetically determined lipoprotein that structurally appears to be an LDL particle with a large glycoprotein (apo A) attached through a disulfide link to apo B. Epidemiologic evidence has generally suggested that Lp(a) concentrations > 25 mg/dL are associated with increased CHD and cerebrovascular disease risk. Also, there is evidence that the apo A glycoprotein has structural homology to plasminogen and, as a result, may interfere with fibrinolysis. This property contributes to a postulated dual functional role of Lp(a), participating in atherogenesis as an LDL-like particle and participating in acute thrombosis formation, which usually occurs on disrupted atherosclerotic plaques. The risk for CHD with increased Lp(a) is enhanced by elevated LDL-C, and some clinical evidence suggests that Lp(a) may cease to be a risk factor when LDL-C levels are sufficiently lowered. Treatment to lower Lp(a) is limited to high-dose niacin (3 to 4 g/d), oral estrogen, and LDL apheresis.

There is no consensus for the clinical scenarios in which measurement of Lp(a) would be helpful for risk discrimination. It may be clinically useful to screen for Lp(a) in primary prevention patients with very strong family histories of premature CHD to document possible genetic determinants of CHD risk. Because some studies have suggested that aggressive LDL-C reduction ameliorates the risk from a high Lp(a), there is no need to measure Lp(a) in CHD patients, who will already be candidates for such LDL-lowering drug treatment. Note that Lp(a) measurements currently are not standardized and are considered a research tool. Further studies on Lp(a)'s origin, metabolism,

physiologic functions, and modulation of its serum concentration are needed before routine use of this risk factor can be recommended.

NONLIPID RISK FACTORS

There is considerable interest among clinicians about the role of such nonlipid risk factors for CHD as homocysteine and fibrinogen. Several epidemiologic studies have demonstrated a strong, positive-graded relationship between total plasma

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homocysteine and vascular disease. One prospective study of CHD patients observed for 4.6 years showed a graded relationship between the plasma homocysteine level and all-cause mortality. The US Physicians Health Study found that elevated total homocysteine levels in men afforded a 3.4-fold greater incidence of myocardial infarction than normal levels. Although there is no consensus, homocysteine levels > 10 μ mol/L are considered elevated. The mechanism(s) that are responsible for this association between homocysteine and atherosclerosis are not completely understood; however, several candidate effects have been proposed. Homocysteine impairs endothelial function and reduces nitric oxide formation, most likely by facilitating the formation of reactive oxygen-derived substances. These reactive substances increase oxidative stress and may enhance the oxidation of lipoproteins, particularly LDL. Homocysteine enhances platelet aggregability and has been shown to stimulate smooth muscle cell proliferation.

In order to understand the causes of elevated

plasma homocysteine, one needs to examine its formation and metabolism. Homocysteine is an intermediate product generated by demethylation during the metabolism of the essential amino acid methionine. It has two metabolic fates: One is remethylation back to methionine, which requires methylenetetrahydrofolate reductase, a folate- and pyridoxine (vitamin B₆)-dependent enzyme; the other is transsulfuration to cysteine through the enzyme cystathionine β -synthase, which is pyridoxine dependent. Both pyridoxine and folate are important nutritional cofactors in homocysteine metabolism. Deficiencies of these vitamins can increase homocysteine levels, and supplementation with high doses can lower elevated homocysteine values. Because these vitamins are safe and inexpensive, it has been suggested that supplementation with 1 to 2 mg/d of folate and/or 50 to 100 mg/d of pyridoxine might be used empirically in all high-risk primary and secondary prevention patients without measuring baseline homocysteine. There are no standards for homocysteine measurement and, as yet, no clinical trial data to support treatment efforts.

Fibrinogen is a strong predictor for cardiovascular disease and total mortality in healthy and CHD patients. Most epidemiologic studies demonstrate that patients in the highest tertile of fibrinogen levels compared with the lowest had a two to three times greater incidence of major cardiovascular events. Fibrinogen is obviously important in the thrombotic cascade that occludes arteries when atherosclerotic plaques rupture. Unfortunately, there are few reliable treatments that substantially reduce fibrinogen, and measurements

are not standardized. At the present time, measurement of fibrinogen as a risk discriminator cannot be recommended in primary or secondary prevention.

CLINICAL MANAGEMENT OF DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS

The NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents has published guidelines for the management of dyslipidemias in young people (aged 2 to 19 years) (Table VIII). The panel's screening recommendations are selective rather than universal. If a parent has a total cholesterol ≥ 240 mg/dL, then the child, adolescent, or young adult should have a screening total cholesterol level. A full fasting lipoprotein profile is performed if the pediatric patient has a total

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cholesterol > 200 mg/dL or has a family history of premature CHD (especially in a parent) or a familial dyslipidemia. The total cholesterol and LDL-C cut-points are lower for pediatric patients than for adults. Acceptable, borderline-high, and

TABLE VIII.

NCEP RECOMMENDED TOTAL CHOLESTEROL AND LDL CHOLESTEROL CUT-POINTS FOR CHILDREN AND ADOLESCENTS

<i>Risk</i>	<i>Total Cholesterol (mg/dL)</i>	<i>LDL Cholesterol (mg/dL)</i>
Acceptable	< 170	< 110
Borderline-high	170–199	110–129
High	≥ 200	≥ 130

NCEP = National Cholesterol Education Program. Data from the National Cholesterol Education Program (Adult Treatment Panel II). *JAMA*. 1993;269:3015–3023.

high values are < 170, 170 to 199, and ≥ 200 mg/dL for total cholesterol, and < 110, 110 to 129, and ≥ 130 mg/dL for LDL-C. As in adults, HDL-C is considered significantly low if it is < 35 mg/dL. Any intervention based on these cut-points applies only to young people from families with premature CHD or genetic dyslipidemias. As for adults, secondary causes should be considered, with the most common being high-fat diet, obesity, oral contraceptives, isotretinoin, and anabolic steroids. The most common genetic causes of elevated LDL-C are heterozygous FH and familial combined hyperlipidemia. Clinical findings such as vascular bruits, xanthelasma, arcus cornealis, and tendinous xanthomas are much less prevalent in young people than in adults with these genetic hypercholesterolemias. Treatment should always focus on a healthy lifestyle, including a low-fat diet, weight control, regular exercise, and avoidance of tobacco. Pharmacologic intervention may be used after puberty in unusual cases, such as severe LDL-C or triglyceride elevations.

LIPID SCREENING IN SPECIAL POPULATIONS

As has been previously discussed, the NCEP ATP II recommends that all adults over age 20 obtain a screening total cholesterol and HDL-C. The panel's recommendations for intensive lifestyle and possibly drug intervention to reduce CHD risk depend on whether a patient has either several risk factors (including age) for primary prevention or documented CHD for secondary prevention. These two recommendations seem to be contradictory because it would appear that screening for cholesterol should not be done in everyone over age 20,

only in those for whom treatment has been documented to reduce CHD events. Young adults, such as men under 40 years of age and premenopausal women, are usually at low risk for near-term CHD events, frequently do not have multiple CHD risk factors, and have never been studied in CHD prevention trials. The American College of Physicians has used this logic to recommend that routine cholesterol screening not be performed in young men and women, with the exception of those with multiple risk factors (including a strong family history of CHD and/or dyslipidemia). While this approach may have some merit, it eliminates the opportunity to use cholesterol screening as a springboard for discussing the health benefits of low-fat diets, exercise, and weight control with young adults.

At the other end of the age spectrum are older men and women (over 70 years of age) without known CHD or vascular disease. There is some controversy as to whether these patients should be screened. Because there are no convincing treatment trials demonstrating a primary prevention benefit of cholesterol lowering in people 75 years and older, the NCEP ATP II has left screening decisions to the practitioner, based on the patient's general health and presence of comorbid illnesses. Clearly, the presence of other significant noncardiovascular diseases may play a greater role in determining near-term morbidity and mortality, and cholesterol screening would not greatly affect overall outcome. In otherwise healthy, older individuals, cholesterol screening can be used as an opportune time to make and reinforce healthy lifestyle recommendations.

CONCLUSION

The wealth of clinical trial evidence that has established the morbidity and mortality benefits of lowering total cholesterol and LDL-C in high-risk individuals makes it imperative for primary care physicians to become familiar with the clinical diagnosis of dyslipidemias. The NCEP ATP II guidelines for screening adults in primary prevention and for treatment goals in secondary prevention are critical to the appropriate management of CHD risk. The cost-effectiveness of preventing

KEY POINT

subsequent acute CHD events in secondary prevention is unquestionable. On the other hand, the cost-effectiveness of primary prevention depends on the physician's ability to identify the patient who not only has a significant dyslipidemia, but has other established risk factors as well. If we are ever going to significantly reduce the prevalence of CHD in the United States, it will be through well-devised primary prevention strategies.

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Dialogue Box

ADVISORY BOARD

When the primary care physician determines the cardiovascular lipid profile of a patient, are there any special instructions regarding medications or diet that should be given the patient other than the requirement for a 12- to 16-hour fast?

JONES

From the patient's standpoint, dietary indiscretion plays a small, short-term role in LDL levels. Depending on their propensity for having triglyceride abnormalities, a patient's change in diet for 3 or 4 days could influence the triglyceride level

in the short run. Vitamin intake does not really matter and any other medication that the patient is taking will not influence the fasting lipid values. Basically, we tell patients not to come to the lab after having an extravagant dietary weekend, drinking a lot of alcohol, or after a sudden alteration in diet. Just eat like you do normally, don't do anything different, and that should result in a pretty accurate cholesterol test.

ADVISORY BOARD

Why did you choose to include the Fredrickson and Lees classification system and what clinical implications does it hold?

Dialogue Box

JONES

For all intents and purposes, the Fredrickson and Lees classification has no real clinical value in the patient with elevated serum cholesterol and a serum triglyceride level below 400; management of such a patient is based primarily on the LDL-cholesterol as stipulated in the NCEP guidelines.

However, for the subset of patients with elevated cholesterol and serum triglycerides above 400, and in whom LDL-cholesterol cannot be calculated, an understanding of the Fredrickson and Lees classification is important since, as demonstrated in Table IV, the risk of coronary artery disease varies depending on the lipoprotein type. For example, hypercholesterolemic patients with an elevated serum triglyceride level above 400 could fall into type II-b or III, be at increased risk for coronary artery disease, and warrant aggressive management of their hypercholesterolemia and other atherosclerotic risk factors. On the other hand, such a patient might also be classified as type IV, be at no increased risk for coronary disease, and warrant treatment of the hyperlipidemia based solely on the level of hypertriglyceridemia and the risk of associated complications such as pancreatitis.

Classification of many of these hypercholesterolemic patients (with high serum triglycerides and in calculable LDL-cholesterol) into their Fredrickson and Lees lipoprotein types can be accomplished by scoring the severity of their lipid abnormalities and seeing in which group in Table IV they are the closest match for. It should be noted, however, that the overlap of triglyceride and cholesterol values can, in some patients, obscure the important distinction between type III (increased risk for coronary artery disease) and type IV (no increased risk for coronary artery disease). In such patients, lipoprotein electrophoresis should be obtained to make this important clinical distinction.

ADVISORY BOARD

What is the association between elevated triglycerides and small, dense LDL?

JONES

The triglyceride level alone does not tell you what is going on with HDL or LDL particle size or composition. All you can say is that as the total cholesterol begins to rise along with any given triglyceride level, the risk of having small, dense LDL increases. That is what we call combined hyperlipidemia, a situation in which triglyceride levels are > 200 but < 1000 mg/dL, and the cholesterol is above 200 mg/dL. We don't know what part of that > 200 is LDL cholesterol.

ADVISORY BOARD

Is there a way to determine the particle size of LDL in patients with hypertriglyceridemia?

JONES

Without the ability to do a fairly sophisticated PAGE (polyacrylamide gel electrophoresis), there is no easy clinical way to separate small, dense LDL from "normal"-sized LDL. However, using apoprotein B can be helpful. If two patients have exactly the same cholesterol and triglyceride levels, but one has a "normal" apo B and the other a high apo B measurement, the high apo B person is probably the one with the small, dense LDL. Apo B is easier to measure and more available to most practitioners than PAGE.

ADVISORY BOARD

Consider a case in which the patient's LDL is below the NCEP threshold for drug therapy, but the triglyceride remains above 200 mg/dL despite lifestyle intervention. Would you treat with drugs?



Dialogue Box

JONES

If the patient's triglycerides are ≥ 1000 mg/dL, I would treat because of the risk for pancreatitis. If they are below that level but above 200 mg/dL, the decision to use drug therapy would depend on the status of the other risk factors. Let's say a 40-year-old male patient presents in clinic with a cholesterol level of 200, triglycerides of 400, and an HDL of 35 mg/dL. Furthermore, he says that every man in his family dies of a massive myocardial infarction by age 50. That is a terrible family history and this patient does not have a normal lipid profile. His LDL is not elevated, but at his age, and with his family history, it is hard to ignore his lipid abnormality. Because the rest of the family are deceased, we can't determine whether there is a genetic link. Under those circumstances, I would seriously consider treating him, probably with a fibric-acid derivative or niacin. On the other hand, if a 40-year-old man with the same lipid profile exercises and has no other risk factors or family history, I would not consider him a candidate for lipid-lowering therapy.

ADVISORY BOARD

Let's say you have the same situation, but the patient's LDL is approaching the level where the NCEP guidelines recommend considering drug therapy. Would you use the same treatment? Would there be any point in using combination therapy?

JONES

In such a case, I would probably focus the drug treatment choice on a statin.* Some clinical data suggest that in people who have high LDL in the treatable range, lowering the LDL still gives clinical benefit when there is a concomitant mild triglyceride elevation.

Combination therapy is always a consideration, depending on the triglyceride levels. If the

levels are in the higher hundreds, I would worry about the triglyceride value even if the total cholesterol and LDL were appropriately treated. If a person has known coronary disease, any abnormality with HDL, LDL, or triglycerides needs to be treated. In this case, combination therapy would be a great idea. First, I would focus on lowering the LDL, but if I don't get the triglycerides down or the HDL up enough, I would probably move to an added drug. In the case of primary prevention, I might not be as aggressive with combination therapy.

ADVISORY BOARD

The ACP has come up with guidelines saying that screening is not mandated in men under 35 and premenopausal women. What are your opinions on screening in young people?

JONES

I like the idea of doing a lipid screen. It is fairly inexpensive, and everybody should know their cholesterol and HDL levels at least once before they get to be a postmenopausal woman or a man 40 years of age. Based on the results we obtain, we should follow the NCEP guidelines. The main reason we screen is to use cholesterol as an incentive to get people to do what they are supposed to do with lifestyles. I can't tell you how many times patients respond to that. You say, "Lose weight, change your diet," and they brush it off; then you give them an abnormal cholesterol level and they say, "Maybe I do need to get serious." If a significant lipid abnormality is found, a clinician may be encouraged to prescribe drug therapy since that is the easiest thing to do. However, the NCEP would say, "Wait a minute, don't do that." We don't have the clinical data to say that using drugs to treat these people in the next 5 years is going to make a difference in their coronary event rates. The point should be that screening allows

*HMG-CoA reductase inhibitors have not been approved by the FDA for treatment of hypertriglyceridemia.



Dialogue Box

you to identify them, and you have made them aware of the situation. You know they are not going to get lost in the follow-up, and this lipid condition is not going to be ignored until they have their first MI. So I favor screening even in young people for the purpose of reinforcing lifestyle. At the same time, we must remember that drug treatment is not indicated in this population because of a lack of clinical trials.

ADVISORY BOARD

What are your thoughts about screening in the elderly population?

JONES

There are no data on primary prevention in patients over age 75. In this population, patients often want to know what their cholesterol is, and it is easy to do. It is part of most profiles you get on patients. If a man or woman over age 75 presents with a high cholesterol, say 265 mg/dL, but they don't have any vascular disease, chances are that the patient has high HDL as part of their high cholesterol. That is probably why they made it this far in life without vascular disease. The high cholesterol could also be a marker of sub-clinical hypothyroidism. This should be treated instead of worrying about the cholesterol. Also, patients in this age-group tend to be more compliant with a physician's recommendations than, say, a 35-year-old. I reinforce the need to

work with diet and exercise, but I rarely treat them with drugs.

ADVISORY BOARD

Let's say a patient is newly diagnosed with diabetes. Before you gain good metabolic control of the disease, you find that the patient's lipids are abnormal. Would you suggest optimizing diabetic control before launching into drug therapy for hyperlipidemia? Or would you do the two concurrently?

JONES

I think it depends on where they start. For instance, if a diabetic patient presents with questionable glucose control but his or her triglycerides are very high—over 1000 mg/dL—no matter how hard you try to control the diabetes, that patient's triglycerides are not going to normalize. Usually, patients with diabetes and very high triglycerides have both a genetic predisposition and poor glucose control. On the other hand, triglycerides of 200 to 1000 mg/dL could be markedly improved and almost normalized by glucose control. If you see a high LDL despite dietary and other lifestyle changes, just improving the glucose level is not going to make much impact on the cholesterol. I would probably initiate lipid-lowering treatment pretty early based on the patient's LDL and other risk factors.

Exhibit B: Sempos et al., *JAMA* 269(23):3009-3014 (1993)

Prevalence of High Blood Cholesterol Among US Adults

An Update Based on Guidelines From the Second Report of the National Cholesterol Education Program Adult Treatment Panel

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Objective.—To estimate the current levels and trends in the proportion of US adults with high blood cholesterol based on guidelines from the second report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP II).

Design.—Nationally representative cross-sectional surveys.

Setting/Participants.—Data for 7775 participants 20 years of age and older from phase 1 of the third National Health and Nutrition Examination Survey (NHANES III) (data collected from 1988 through 1991) and for 9797 participants 20 through 74 years of age from NHANES II (data collected from 1976 through 1980) were used.

Results.—From the data collection period in NHANES II (1976 through 1980) to the period in NHANES III (1988 through 1991), the proportion of adults with high blood cholesterol levels (≥ 240 mg/dL [6.21 mmol/L]) fell from 26% to 20%, while the proportion with desirable levels (< 200 mg/dL [5.17 mmol/L]) rose from 44% to 49%. Currently, using the ATP II guidelines and NHANES III data, 40% of all adults 20 years of age and older would require fasting lipoprotein analysis; and 29% of all adults would be candidates for dietary therapy (as compared with 36%, using NHANES II data). Based on 1990 population data, it is estimated that approximately 52 million Americans 20 years of age and older would be candidates for dietary therapy. Assuming that dietary intervention would reduce low-density lipoprotein (LDL) cholesterol levels by 10%, as many as 7% of all adult Americans (approximately 12.7 million) might be candidates for cholesterol-lowering drugs. This estimate reflects approximately 4 million adults with established coronary heart disease, of whom half are aged 65 years and older, and up to 8.7 million adults without established coronary heart disease, of whom up to 3.1 million are aged 65 years and older.

Conclusions.—Substantial progress has been made in reducing the prevalence of high blood cholesterol; yet a large proportion of all adults, approximately 29%, require dietary intervention for high blood cholesterol.

(*JAMA*. 1993;269:3009-3014)

THE NATIONAL Heart, Lung, and Blood Institute launched the National Cholesterol Education Program (NCEP) in 1985.^{1,2} The goal of the program is to reduce the prevalence of elevated blood cholesterol levels in the United States, thereby contributing to the reduction of coronary heart disease (CHD) morbidity and mortality. As part of its activi-

ties, the NCEP established the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP I]),³ which focuses on the application of the clinical, patient-based approach to the prevention of CHD. Since ATP I, scientific progress and 5 years of experience with the guidelines prompts an updating. The second report of the Adult Treatment Panel (ATP II) is similar to ATP I in its outline and fundamental approach to the treatment of high blood cholesterol.⁴ It continues to identify low-density lipoprotein (LDL) cholesterol as the primary target for cholesterol-lowering therapy; dietary therapy remains the initial and principal mode of treatment; and drug therapy is reserved for patients at high risk of CHD.

There are several new features in ATP II: lower LDL cholesterol goals and initiation levels have been established for those with existing CHD; more attention has been given to high-density lipoprotein (HDL) cholesterol as a CHD risk factor; high-risk postmenopausal women and high-risk elderly patients who are

See also pp 3002 and 3015.

otherwise healthy are recognized to be candidates for cholesterol-lowering therapy; and more explicit reservations have been expressed concerning the use of drug therapy in young adult men and premenopausal women with high LDL cholesterol who are otherwise at low short-term risk of CHD.

The potential impact of the ATP II guidelines in US adults was previously evaluated using data collected from 1976 through 1980 as part of the second National Health and Nutrition Examination Survey (NHANES II).⁵ It was then estimated that 41% of US adults would require lipoprotein analysis and that 36% (approximately 60 million adults) would require dietary therapy. More recent national data from NHANES III (data collected from 1988 through 1991) have documented a continued decline in serum total cholesterol levels.⁶ This article applies the ATP II guidelines to the NHANES data to examine the current levels and trends in the percentage of US adults 20 years of age and older who would require fasting lipoprotein analysis, and the percentage and number of adults who would be candidates for medical advice and intervention, using dietary therapy with or without drug treatment.

METHODS

Data Sources

The NHANES are designed to produce nationally representative data regarding the civilian, noninstitutionalized US population. They are conducted by

From the Division of Health Examination Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Md (Drs Sempos and Briefel, Mss Carroll and Burt, and Mr Johnson); the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md (Drs Cleeman, Gordon, Lippel, and Rifkind, and Ms Brown); and The Johns Hopkins Hospital, The Children's Medical and Surgical Center, Baltimore, Md (Dr Bachorik).

Reprint requests to the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health, Bldg 31, Room 4A-05, Bethesda, MD 20892 (Dr Cleeman).

the National Center for Health Statistics, Centers for Disease Control and Prevention. Data from two NHANES are used in this report. Current estimates are based on the latest national data from NHANES III.⁷ Trends in the estimates are based on comparisons with NHANES II.⁸

There are some differences between the two surveys. There is no upper age bound for inclusion in NHANES III, while the upper age bound for NHANES II was 74 years. Also, NHANES III was designed to produce national estimates for Mexican Americans in addition to those for black and white Americans. Race was self-reported in NHANES III and observed in NHANES II. In NHANES III, blood pressure was measured three times as part of the initial household interview and three more times during the subsequent medical examination. In NHANES II, it was measured three times during the medical examination.

Sample persons were asked about their history of heart attack, stroke, and diabetes.^{8,9} Current use of cigarettes and of lipid-lowering and antihypertensive medications was also ascertained. The Rose Questionnaire for Angina Pectoris¹⁰ was administered to all adults in NHANES III and to those 25 years of age and older in NHANES II. Blood pressure in both surveys was measured using procedures outlined by the American Heart Association.^{11,12}

Laboratory Methods

The laboratory methods are described in detail by Johnson et al.⁶ Briefly, all lipid measurements were based on a single blood determination. Data for total and HDL cholesterol were available for 7775 sample persons in NHANES III (6727 aged 20 through 74 years) and for 9797 in NHANES II. Fasting serum triglyceride levels (≥ 9 hours) for a random sample of those examined were available from 3342 sample persons in NHANES III (2942, aged 20 through 74 years) and 3593 in NHANES II. The LDL cholesterol level was calculated using the equation developed by Friedewald.¹³

Issues concerning the comparability of the laboratory data collected in NHANES II and NHANES III were examined in detail by Johnson et al.⁶ In summary, the data appear to be comparable.

The ATP II Guidelines

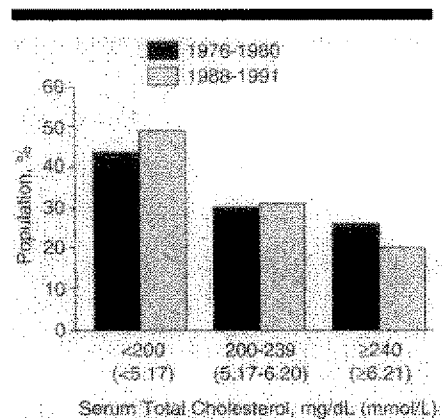
The ATP II guidelines are described, in detail in this issue of THE JOURNAL.⁴ In brief, the ATP II report initially classifies adults by the presence or absence of CHD. In patients without CHD, the guidelines recommend the measurement

of nonfasting total and HDL cholesterol levels, which (with assessment of a patient's nonlipid risk factors) are used to identify those patients who require fasting lipoprotein analysis. Persons with no CHD who have any of the following require fasting lipoprotein analysis: (1) total cholesterol level of 240 mg/dL (6.21 mmol/L) and higher; (2) HDL cholesterol level less than 35 mg/dL (0.91 mmol/L); or (3) total cholesterol level between 200 and 239 mg/dL (5.17 through 6.20 mmol/L) and two or more CHD risk factors. Those with existing CHD require fasting lipoprotein analysis regardless of their blood cholesterol level.

The risk factors designated by the ATP II for consideration when interpreting blood cholesterol levels comprise the following: (1) age; male 45 years and older, female 55 years and older or having premature menopause without estrogen replacement therapy; (2) family history of premature CHD; (3) current cigarette smoking; (4) hypertension (ie, blood pressure of 140/90 mm Hg and higher) or use of antihypertensive medications; (5) HDL cholesterol level less than 35 mg/dL (0.91 mmol/L); and (6) diabetes mellitus. One risk factor is subtracted if HDL cholesterol levels are 60 mg/dL (1.55 mmol/L) and higher.

Individuals who require lipoprotein analysis are then classified on the basis of the presence or absence of CHD, their LDL cholesterol levels, and their other CHD risk factors. In persons without evidence of CHD, those with LDL cholesterol levels of 160 mg/dL (4.14 mmol/L) and higher and those having LDL cholesterol levels between 130 and 159 mg/dL (3.36 through 4.13 mmol/L) who have two or more CHD risk factors would be candidates for dietary intervention. In adults with evidence of CHD, those with LDL cholesterol values greater than 100 mg/dL (2.59 mmol/L) would also be candidates for dietary intervention.

After an adequate trial of dietary modification, consideration may be given to drug therapy if LDL cholesterol levels remain 30 mg/dL (0.78 mmol/L) higher than the initiation levels. Thus, ATP II LDL cholesterol levels for considering drug therapy comprise the following: (1) 190 mg/dL (4.91 mmol/L) and higher for persons without CHD and with fewer than two CHD risk factors; (2) 160 mg/dL (4.14 mmol/L) and higher for persons with two or more CHD risk factors; and (3) 130 mg/dL (3.36 mmol/L) and higher for patients with existing CHD. Men younger than 35 years of age and women younger than 55 years of age with LDL cholesterol levels between 190 and 219 mg/dL (4.91 through 5.66 mmol/L) who do not have CHD or multiple CHD risk



Age-adjusted serum total cholesterol levels of the US population aged 20 through 74 years for 1976 through 1980 (unpublished data from the second National Health and Nutrition Examination Survey [NHANES II]) and 1988 through 1991 (unpublished data from NHANES III).

factors would not generally be candidates for drug therapy unless they have a particularly increased risk of CHD.

Application of the ATP II Guidelines to NHANES III and NHANES II

In applying the ATP II guidelines to NHANES data, definite CHD was defined as a positive response to the Rose Questionnaire for Angina Pectoris¹⁰ or a reported history of heart attack.^{8,9} Diabetes mellitus was defined as reported history. In NHANES III, data are not yet available to evaluate menopausal status or possible use of estrogen replacement therapy. Family history of premature CHD was defined as a reported heart attack in a first-degree relative before the age of 50 years. Data were available in NHANES II to determine the presence or absence of all the risk factors except family history of premature CHD.

Because of within-person variability in serum lipids, both the ATP II and the ATP I guidelines specify that all treatment decisions for an individual patient should be based on the average of two (and in some cases three) measurements, with all repeated measurements made 1 to 8 weeks apart.^{3,4} However, the effect of within-person variation on population prevalence estimates based on a single measurement of serum lipids has been shown to be minimal.^{5,14}

Data Analysis

All results from NHANES III and NHANES II are based on the sample weights to produce national estimates. For analyses focusing on current levels using NHANES III data, all available data for the entire age range were used in the data analysis (eg, mean blood pres-

Table 1.—Percentage of US Population Aged 20 Years and Older Who Require Fasting Lipoprotein Analysis*

Population Group	Do Not Require Fasting Analysis		Require Fasting Analysis					CHD	Total§
	Desirable (<200 mg/dL [<5.17 mmol/L]; HDL ≥ 35 mg/dL [≥ 0.91 mmol/L])	Borderline-High (200-239 mg/dL [5.17-6.20 mmol/L]; HDL ≥ 35 mg/dL [≥ 0.91 mmol/L]; <2 RFs)	Borderline-High			High (≥ 240 mg/dL [≥ 6.21 mmol/L])			
			Desirable (<200 mg/dL [<5.17 mmol/L]; HDL <35 mg/dL [<0.91 mmol/L])	(200-239 mg/dL [5.17-6.20 mmol/L]; HDL ≥ 35 mg/dL [≥ 0.91 mmol/L]; ≥ 2 RFs)	(200-239 mg/dL [5.17-6.20 mmol/L]; HDL <35 mg/dL [0.91 mmol/L])				
All persons	41	19	4	7	3	18	7	40	
Ethnicity									
Mexican American	46	20	5	5	3	15	6	34	
Non-Hispanic black†	45	20	3	7	2	16	7	35	
Non-Hispanic white†	40	19	5	7	4	19	8	42	
Race‡									
Black	46	20	3	7	2	16	7	34	
White	40	19	4	7	4	19	7	41	
Sex/age, y									
Men									
≥20	39	18	6	7	5	17	8	44	
20-34	58	20	7	2	3	9	2	23	
35-44	37	25	6	2	7	18	3	38	
45-54	25	14	5	14	7	25	9	61	
55-64	19	13	3	15	7	25	17	68	
65-74	22	9	7	16	6	22	17	69	
≥75	31	11	6	11	3	14	23	58	
Women									
≥20	43	20	2	6	1	20	7	36	
20-34	65	17	4	2	1	8	3	18	
35-44	53	24	3	3	3	11	4	24	
45-54	36	30	0	5	1	23	6	34	
55-64	17	19	1	13	2	37	12	64	
65-74	17	18	2	14	0	39	11	65	
≥75	22	12	2	13	1	32	16	65	

*Using initial classification based on total and high-density lipoprotein (HDL) cholesterol levels, presence of coronary heart disease (CHD), and risk factors (RFs) for CHD. Unpublished data from the third National Health and Nutrition Examination Survey.

†All Hispanic persons were excluded.

‡Includes Hispanic persons.

§Rows may not sum to the total due to rounding.

sure was the average of as many as six blood pressure measurements). For trends analyses, age was restricted to 20 through 74 years, family history of premature CHD was not included as an ATP II risk factor, angina was evaluated for ages 25 through 74 years, mean blood pressure was the average of the three readings (household readings in NHANES III and mobile examination center readings in NHANES II), and data were age-adjusted using the direct method to the total adult population for 1980.

To simulate the effect of dietary modification on the potential percentage of adults who might require drug therapy, the LDL cholesterol levels of the candidates for dietary intervention were reduced by 5%, 10%, or 15%, and the resultant values were compared with the guidelines for consideration of drug therapy. Population estimates for 1990, age- and sex-specific dietary therapy intervention rates, and age- and sex-specific drug treatment intervention rates (assuming an average 10% reduction in LDL cholesterol due to dietary modification) were used to estimate the total

number of adults, in millions, who might be candidates for medical advice and intervention using dietary modification and drug treatment.

RESULTS

During the period from NHANES II (1976 through 1980) to NHANES III (1988 through 1991) there was a substantial downward shift in the age-adjusted distribution of serum total cholesterol (Figure). The age-adjusted proportion of adults 20 through 74 years of age with serum total cholesterol levels of 240 mg/dL (6.21 mmol/L) and higher decreased from 26% to 20% (men, 25% to 19%; women, 28% to 20%), while the proportion with levels lower than 200 mg/dL (5.17 mmol/L) increased from 44% to 49% (men, 44% to 48%; women, 43% to 50%). The proportion with levels between 200 and 239 mg/dL (5.17 and 6.20 mmol/L) increased slightly from 30% to 31% (men, 31% to 33%; women, 29% to 30%). The decreases in the age-adjusted percentage with high cholesterol levels were similar for blacks and whites, although there appeared to be a larger shift for whites toward desirable levels (data not shown).

When the ATP II guidelines were applied to the NHANES III data, it was estimated that 40% of adults would require lipoprotein analysis (Table 1), of whom about one sixth (7%/40%) had existing CHD. More than half of the remainder (18%/33%) had high blood cholesterol levels (240 mg/dL [6.21 mmol/L] and higher), while the rest had borderline-high cholesterol levels (200 through 239 mg/dL [5.17 through 6.20 mmol/L]) with multiple nonlipid CHD risk factors (7%) or HDL cholesterol levels lower than 35 mg/dL (0.91 mmol/L) (7%). The rates of lipoprotein analysis were about eight percentage points lower in Mexican Americans and blacks than in whites. They were also slightly higher for men than for women.

Approximately 29% of all adults 20 years of age or older (74% of those requiring fasting lipoprotein analysis) would be candidates for dietary therapy (Table 2). Six of seven of those with preexisting CHD would be candidates for intervention. More than two thirds of the candidates for dietary therapy who did not have established CHD (16%/23%) came from those with high-risk LDL chole-

Table 2.—Percentage of US Population Aged 20 Years and Older Who Are Candidates for Dietary Intervention*

Population Group	Not a Candidate for Dietary Intervention			Candidate for Dietary Intervention			Total‡
	Desirable (LDL <130 mg/dL [<3.36 mmol/L])	CHD and LDL ≤100 mg/dL (≤2.59 mmol/L)	Borderline-High-Risk (LDL 130-159 mg/dL [3.36-4.13 mmol/L]; <2 RFs)	Borderline-High-Risk (LDL 130-159 mg/dL [3.36-4.13 mmol/L]; ≥2 RFs)	High-Risk (LDL ≥160 mg/dL [≥4.14 mmol/L])	CHD and LDL >100 mg/dL (>2.59 mmol/L)	
All persons	7	1	2	7	16	6	29 (74)
Ethnicity							
Mexican American	8	1	3	5	12	4	21 (63)
Non-Hispanic black†	4	1	2	7	15	5	27 (78)
Non-Hispanic white†	7	1	2	7	17	6	31 (74)
Race‡							
Black	4	1	2	7	15	5	27 (78)
White	7	1	2	7	17	6	30 (73)
Sex/age, y							
Men							
≥20	9	1	2	9	17	6	32 (74)
20-34	7	0	2	4	9	2	14 (61)
35-44	7	0	3	6	20	2	27 (73)
45-54	12	1	3	13	25	6	45 (74)
55-64	8	2	2	16	26	14	56 (83)
65-74	14	2	0	14	24	15	53 (77)
≥75	7	2	2	14	15	18	47 (81)
Women							
≥20	5	2	3	6	15	6	27 (73)
20-34	5	2	1	2	6	1	9 (51)
35-44	6	1	4	2	5	7	13 (55)
45-54	1	1	2	4	19	7	29 (85)
55-64	5	4	4	12	30	9	52 (80)
65-74	8	1	2	13	35	6	54 (83)
≥75	5	0	2	13	26	18	58 (89)

*Unpublished data from the third National Health and Nutrition Examination Survey. CHD represents coronary heart disease; LDL, low-density lipoprotein; and RF, risk factor for CHD.

†All Hispanic persons were excluded.

‡Includes Hispanic persons.

§Rows may not sum to the total due to rounding. Numbers in parentheses indicate the percentage of those requiring fasting lipoprotein analysis who are candidates for dietary therapy (Table 1).

terol levels (160 mg/dL [4.14 mmol/L] and higher), while the remainder (7%/23%) had borderline-high-risk LDL cholesterol levels (130 through 159 mg/dL [3.36 through 4.13 mmol/L]) and two or more CHD risk factors. Rates of candidacy for dietary intervention were lowest for Mexican Americans (21%), highest for whites (31%), and intermediate for blacks (27%).

Overall, 32% of men and 27% of women would be candidates for dietary intervention (Table 2). The proportions increase substantially with age in both sexes, up to the age category of 55 through 64 years. Below that age category, the gap between men and women is the most pronounced. Above it, the gap narrows and is reversed after the age of 75 years. Beginning with the age category of 55 through 64 years, approximately 50% of all men and women would be candidates for dietary therapy.

Currently, as shown in Table 1, 60% of the total US adult population would not require fasting lipoprotein analysis. Applying the ATP II LDL cholesterol criteria, 4% of that 60% (approximately 2% of the total US adult population) would be candidates for dietary intervention. The two-step process described in ATP II to identify persons who need

dietary therapy identified 94% (29%/31%) of all the persons who would have been identified if the process had begun with fasting lipoprotein analysis.

Based on the ATP II guidelines, the age-adjusted proportion of US adults who would require fasting lipoprotein analysis (calculated for ages 20 through 74 years in both NHANES II and NHANES III) dropped from 44% in NHANES II to 37% in NHANES III, and the proportion who would be candidates for dietary therapy decreased from 35% to 27%. The declines were similar for blacks and whites, but were greater in women than in men (data not shown).

For people who require intervention for high blood cholesterol, the primary method of intervention is dietary therapy. However, an important question is, "What proportion of the population might be candidates for drug therapy after an adequate trial of dietary modification?" If it is assumed that dietary intervention would uniformly reduce LDL cholesterol levels by 5%, 10%, or 15%, it is predicted that 10%, 7%, or 5%, respectively, of all adults might require drug treatment after dietary intervention; about 30% to 40% of these individ-

uals have existing CHD (Table 3). The percentage who might require drug therapy is lower for Mexican Americans than for non-Hispanic blacks and for whites. Proportionately, few men younger than 45 years and few women younger than 55 years would require drug treatment. Assuming a 10% reduction in LDL cholesterol levels, approximately half of the rate for men older than 54 years of age is composed of those with preexisting CHD; for women older than 54 years of age, the proportion of the total with preexisting CHD ranges from 25% to 60%.

Using the age- and sex-specific data from Table 2 for the total proportion who are candidates for dietary intervention and similar data from Table 3 and assuming a uniform 10% reduction in LDL cholesterol levels due to dietary modification, the number of adults 20 years of age and older who might require dietary modification and drug therapy was estimated. Based on the 1990 population, it is estimated that approximately 52 million adults require dietary modification for high blood cholesterol. It is also estimated that up to 12.7 million Americans might require cholesterol-lowering drug treatment. This estimate does not take into account the fact that these drugs

Table 3.—Predicted Percentage of US Population Aged 20 Years and Older Who Might Qualify for Drug Treatment After Dietary Intervention*

Population Group	Assumed LDL Cholesterol Reduction After Dietary Modification											
	Pre-Diet			5%			10%			15%		
	CHD			CHD			CHD			CHD		
	No	Yes	Total†	No	Yes	Total†	No	Yes	Total†	No	Yes	Total†
All persons	11	3	14	7	3	10	5	3	7	3	2	5
Ethnicity												
Mexican American	5	3	8	3	2	6	2	2	4	2	2	4
Non-Hispanic black‡	11	3	14	8	3	11	6	2	9	5	2	6
Non-Hispanic white‡	11	3	15	7	3	10	5	3	8	3	2	5
Race§												
Black	10	3	14	8	3	11	6	2	9	5	2	6
White	11	3	15	7	3	10	5	3	7	3	2	5
Sex/age, y												
Men												
≥20	12	3	15	7	3	10	6	2	8	4	2	5
20-34	4	1	4	3	1	4	3	0	3	2	0	2
35-44	11	0	11	5	0	5	3	0	3	2	0	2
45-54	22	2	25	13	2	16	12	2	13	8	2	9
55-64	21	9	30	10	9	19	7	8	15	6	7	12
65-74	20	8	28	12	7	19	9	6	16	6	4	10
≥75	13	11	24	11	10	21	9	7	16	6	4	10
Women												
≥20	10	4	13	6	3	10	4	3	7	3	2	5
20-34	1	0	2	1	0	1	0	0	0	0	0	0
35-44	4	3	7	1	2	4	1	2	3	1	2	3
45-54	8	4	12	5	4	9	2	3	5	2	2	4
55-64	23	7	30	17	6	23	13	5	18	7	5	12
65-74	26	6	32	18	4	21	12	4	16	9	3	11
≥75	22	12	34	14	11	26	9	11	20	6	9	15

*Includes persons with (1) coronary heart disease (CHD) and low-density lipoprotein (LDL) cholesterol level ≥ 130 mg/dL [3.36 mmol/L]; (2) LDL level ≥ 190 mg/dL [4.91 mmol/L], for men ≥ 35 and women ≥ 55 years of age; (3) LDL level ≥ 190 mg/dL [4.91 mmol/L] and two or more CHD risk factors for men < 35 and women < 55 years of age; and (4) LDL level 160 through 189 mg/dL [4.14 through 4.90 mmol/L] and two or more CHD risk factors. Unpublished data from the third National Health and Nutrition Examination Survey.

†Rows may not sum to the total due to rounding.

‡All Hispanic persons were excluded.

§Includes Hispanic persons.

are not recommended by ATP II for sick or infirm older patients, and thus may overstate their potential use in the elderly. This estimate includes approximately 4 million adults with established CHD, of whom 2 million are aged 65 years or more, and up to 8.7 million adults without established CHD, of whom up to 3.1 million are aged 65 years or more.

COMMENT

Comparing data from NHANES II (1976 through 1980) with data from NHANES III (1988 through 1991) reveals there was a substantial decline in mean serum total and LDL cholesterol levels.⁶ The age-adjusted proportion of the adult population with total cholesterol levels 240 mg/dL (6.21 mmol/L) and higher fell to 20%. Moreover, the decline in the proportion of the adult population who would be candidates for dietary therapy—from 35% to 27% for those 20 through 74 years of age—is due principally to the observed decrease in blood cholesterol levels; it is not an artifact of the revision of the ATP guidelines. Two analyses demonstrate this. When the ATP II guidelines were ap-

plied to both NHANES II and NHANES III, there was a net fall of 7% in the proportion of adults who required lipoprotein analysis (44% to 37%) over the 12-year period and a net fall of 8% in the proportion who needed dietary intervention (35% to 27%). Furthermore, when ATP I guidelines were applied to NHANES II data, it was reported that 41% of all adults required lipoprotein analysis and 36% needed dietary therapy.⁵ Those figures indicate that the ATP II guidelines as compared with ATP I may have introduced a net increase of 3% in the rate of lipoprotein analysis (from 41% to 44%) and a 1% fall in dietary therapy rate (from 36% to 35%).

Despite declining serum cholesterol levels, there was little change in the proportion who required fasting lipoprotein analysis under ATP II (40%) compared with ATP I (41%) because of revisions to the ATP I guidelines. Under ATP II, persons with existing CHD or a low HDL cholesterol level (less than 35 mg/dL [0.91 mmol/L]) are now referred for lipoprotein analysis regardless of their total cholesterol level; a risk factor is subtracted for a high HDL cho-

lesterol level (higher than 60 mg/dL [1.55 mmol/L]), and age (defined differently for men and for women) is now a risk factor (whereas in ATP I, male sex was considered a risk factor and age was not specifically considered). These changes were intended to better define and identify all those who may be at higher risk of CHD, and who, as a result, require fasting lipoprotein analysis and further medical evaluation. Furthermore, the two-step process of a nonfasting measurement of total and HDL cholesterol levels followed by a fasting lipoprotein analysis identified 94% (29%/31%) of all the US adults who would have met the ATP II guidelines for dietary therapy if fasting lipoproteins had been measured initially in all adults.

More men (32%) than women (27%), at present, are candidates for dietary therapy (Table 2). The large differences between men and women in the proportions who require dietary therapy under the age of 45 years are mainly accounted for by the higher serum total cholesterol levels in men under age 45 years than in women.⁶ In the 45- through 54-year age group, differences in mean serum total

cholesterol levels between men and women are not evident, and the differences in dietary therapy rates can be accounted for by lower HDL cholesterol levels in men and the fact that age becomes a risk factor for men at this point. After 55 years of age, there is a crossover in mean levels of serum cholesterol which, along with age now being a risk factor for women, leads to a narrowing of the gap between men and women and eventually to women having higher rates of candidacy for dietary therapy than men for those older than 75 years of age.

There are also significant differences in the proportion who are currently candidates for dietary therapy among different ethnic groups. The proportion for Mexican Americans is 10 percentage points lower than the proportion for non-Hispanic white Americans. Lower mean serum total and LDL cholesterol levels⁶ probably account for much of the differences, but a complete understanding of the difference awaits the completion of a detailed analysis of the lipid and lipid-related data from both NHANES III and the Hispanic Health and Nutrition Examination Survey (data collected from 1982 through 1984), which is currently under way.¹⁵

According to the ATP II guidelines, after an adequate trial of dietary therapy, consideration may be given to drug treatment if LDL cholesterol levels remain substantially (30 mg/dL [0.78 mmol/L]) higher than initiation levels for dietary therapy. In this article, we report that less than one fourth (7%/29%) of those who require dietary therapy might be considered for drug treatment. Three percent of men younger than 45 years of age and between 3% and 5% of women younger than 55 years of age are predicted to be potential candidates for drug treatment. The values for those over 65 years of age are probably an overestimate, since further analysis is necessary to exclude individuals who, because of illness or infirmity, may not be appropriate candidates for cholesterol-lowering drugs. These relatively low estimates reflect the intent of the guidelines to maximize diet therapy and to reserve potentially costly drug treatment for high-risk patients.

The estimate of the numbers of adults who might need drug treatment is based on the assumption of a 10% reduction in LDL cholesterol attributable to dietary therapy. Several large-scale diet studies in free-living populations have achieved 10% to 15% reductions in serum total cholesterol^{16,17} compared with about 15% to 25% in controlled metabolic ward studies, probably because of less vigorous adherence to diet. The percentage reductions are usually greater

if expressed in terms of LDL cholesterol than total cholesterol. It has been recently suggested that diets lower in saturated fat and dietary cholesterol than the Step 1 Diet (which involves an intake of saturated fat of 8% to 10% of energy intake or calories, $\leq 30\%$ of calories from total fat intake, and cholesterol intake of <300 mg/24 h⁴) may be necessary to achieve reductions of about 10%.¹⁷

The NHANES III data are the most current national data on the prevalence of high blood cholesterol. Yet, because of certain aspects of NHANES and cross-sectional studies in general, the results presented herein should be interpreted cautiously; they are only estimates. Limitations of the data include the following: the sample size is relatively small for some of the data; the number of persons with clinically apparent CHD or diabetes may have been underestimated (because precise diagnostic information was lacking); and it was not possible to assess peripheral arterial or carotid artery disease. Also, information was collected in NHANES III on family history of premature CHD prior to 50 years of age, which is somewhat different from the definition in ATP II⁴ of an event in a first-degree relative prior to 55 years of age in men and prior to 65 years of age in women. On the other hand, estimating an individual's mean blood pressure with as many as six blood pressure measurements helped to reduce misclassification.

The 1980s saw a marked increase in the amount of cholesterol-related information directed to professionals and the public. These include the inception of the NCEP in 1985, the release of the first set of ATP guidelines by the NCEP in the fall of 1987, and intensified cholesterol education efforts by a range of organizations. The present findings suggest that these efforts have contributed to a substantial reduction in the prevalence of high blood cholesterol.

The Department of Health and Human Services has established prevention objectives for the year 2000.¹⁸ One of those is to reduce the proportion of adults with blood cholesterol levels 240 mg/dL (6.21 mmol/L) and higher to 20% or less. Although this interim goal appears to have been reached, many Americans still have blood cholesterol levels that are too high. The reductions in blood cholesterol, judicious application of the ATP II guidelines by the medical community, and continued efforts by the population at large to reduce intakes of saturated fatty acids and dietary cholesterol and to adopt a more heart-healthy life-style should lead to further reductions in blood cholesterol levels

and, it is hoped, to further reductions in CHD incidence and mortality.

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Exhibit C: Ansell et al., *JAMA* 282(21):2051-2057 (1999)

An Evidence-Based Assessment of the NCEP Adult Treatment Panel II Guidelines

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THE SECOND REPORT OF THE NATIONAL Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II)¹ in 1993 was based on review of observational epidemiology, lipoprotein metabolism, animal studies, and early clinical trials. No clinical trial or meta-analysis had yet demonstrated a reduction in overall mortality. Furthermore, there was concern regarding data suggesting increased noncoronary mortality resulting from drug therapy in some trials. Benefits from pharmacological treatment of lower-risk primary prevention patients could be offset by increased relative risks and costs of therapy. Perhaps most importantly, although studies with the relatively new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) were promising, they were preliminary, and the first large statin trial had not yet been published. For these reasons, the Adult Treatment Panel II (ATP-II) report made relatively cautious recommendations about whom and when to treat, and considered nicotinic acid and bile acid sequestrants preferable to statins in many circumstances.

With the results of several large clinical trials reported after the ATP-II report, it is now possible to assess the recommendations with this additional evidence in mind. In addition, issues addressed in limited fashion or not addressed in the report, such as coronary disease associated with organ transplantation and treat-

Context The Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) was issued without the benefit of multiple recently published large clinical trials.

Objective To analyze the panel's guidelines for treatment of high cholesterol levels in the context of currently available clinical trial results.

Data Sources MEDLINE was searched for all English-language clinical trial data from 1993 through February 1999 relating to the effects of cholesterol treatment on cardiovascular clinical outcomes.

Study Selection Studies that were selected for detailed review assessed the effects of cholesterol lowering on either coronary events, coronary mortality, stroke, and/or total mortality, preferably by randomized, double-blind, placebo-controlled design. Selection was by consensus of a general internist, a lipid clinic director, and a researcher in atherosclerotic plaque biology. A core of 37 of the 317 initially screened studies were selected and used as the primary means by which to assess the guidelines.

Data Extraction By consensus of the group, only prespecified end points of trials were included, unless post hoc analysis addressed issues not studied elsewhere.

Data Synthesis Recent clinical trial data mostly support the Adult Treatment Panel II guidelines for cholesterol management. While existing trials have validated the target low-density lipoprotein cholesterol (LDL-C) goals in the report, studies are lacking that address mortality benefit from reduction below these levels. Few lipid-lowering trials have treated patients with low high-density lipoprotein cholesterol and/or elevated triglyceride levels with LDL-C levels at or below treatment goals.

Conclusions Lipid-lowering therapy generally should be more aggressively applied to patients with diabetes and/or at the time of coronary heart disease (CHD) diagnosis. The evidence for statin use in secondary CHD prevention in postmenopausal women outweighs current evidence for use of estrogen replacement in this setting. Further studies are needed to address the effects of lipid modification in primary prevention of CHD in populations other than middle-aged men and to study markers of lipid metabolism other than LDL-C.

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ment of lipid abnormalities in elderly patients can be examined.

Methods

A group consisting of a general internist, a lipid clinic director/cardiologist, and an atherosclerosis researcher met between February and May 1999 and conducted a review of randomized, controlled clinical trials pertaining to lipid lowering published since 1993. A MEDLINE search of all En-

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glish-language clinical trials assessing the effects of cholesterol treatment on coronary events, coronary mortality, stroke, and/or total mortality was conducted, yielding 317 studies. Studies were limited to human subjects and studies whose primary outcome measurements were biochemical, physiological, and/or angiographic were excluded unless they were believed to offer unique clinical information. Two trials in press at the time of the review were also included. A total of 37 studies (including several studies of the same clinical trial) were included in the review and were considered the primary evidence by which the ATP-II guidelines should be assessed.

Safety

Concern regarding potential adverse effects of lipid-lowering medications prompted the ATP-II to recommend caution in their use in the primary prevention of CHD. Contributing to this cautious approach were (1) the finding of increased risk of accidental and violent death in patients treated for hypercholesterolemia⁷ and (2) reports of increased noncardiovascular death in several lipid-lowering trials. These trials were subsequently reported by Gould et al⁸ to reveal a 30% increase in noncardiovascular mortality and a 17% increase in total mortality with fibrates. Since the ATP-II report's publication, there have been additional trials with fibrates, niacin, resins, and statins showing no increase in noncardiovascular mortality. In a meta-analysis of 29 000 patient-lives in statin monotherapy CHD prevention trials published after the ATP-II report, no increase in noncardiovascular mortality or cancer incidence was seen.⁹

CHD Risk Status as a Guide to Intensity of Therapy

The ATP-II report recommended using CHD risk status as a guide to the intensity of therapy. It divided the population at particular risk for CHD into 3 groups, based on known atherosclerotic disease, multiple CHD risk factors, or isolated hypercholesterolemia without other risk factors. This ap-

proach was based in part on (1) clinical trial evidence demonstrating CHD mortality reduction with cholesterol lowering, (2) the desire to reserve what was considered expensive and potentially risky medical therapy for those at greatest CHD risk, and (3) recognition that at the time of the ATP-II report, total mortality benefit with lipid treatment had not been demonstrated. The target low-density lipoprotein cholesterol (LDL-C) levels were less than 4.14 mmol/L (160 mg/dL) for primary prevention patients with fewer than 2 CHD risk factors, less than 3.37 mmol/L (130 mg/dL) for primary prevention patients with 2 or more additional risk factors, and less than 2.59 mmol/L (100 mg/dL) in secondary prevention. The LDL-C recommendations differed somewhat from European standards, which suggest an LDL-C treatment goal of 3.00 mmol/L (116 mg/dL) in patients (with or without CHD) with greater than 2% per year absolute CHD event rates calculated from the Framingham risk model.¹⁰ Both guidelines emphasize the importance of assessing CHD risk in determining candidates for therapy.

Since the ATP-II report, several trials have demonstrated reduction in both CHD and total mortality with statin therapy. First, the Scandinavian Simvastatin Survival Study (4S) of hyperlipidemic subjects with CHD showed a 30% relative and a 3.3% absolute risk reduction in total mortality with simvastatin therapy for just over 5 years.¹¹ Later, the Long-term Intervention With Pravastatin in Ischaemic Disease (LIPID) study showed a 23% relative and a 3.1% absolute risk reduction in total mortality with pravastatin treatment in a diverse group of CHD patients during a 6-year period.¹² Furthermore, other large trials demonstrated benefit from reduction of cholesterol levels considered to be average in the ATP-II report. In the Cholesterol and Recurrent Events (CARE) trial, pravastatin therapy yielded a 24% relative and a 3.0% absolute risk reduction in fatal CHD events and nonfatal myocardial infarctions (MIs) in CHD patients with "average" total cholesterol levels (mean, 5.41 mmol/L [209 mg/dL]).¹³ In

these trials, clinical event reductions were noted as early as 3 to 6 months in patients receiving drug therapy. The consistent and early benefit of statin therapy in CHD patients strongly suggests beginning lipid-lowering therapy at the time of CHD diagnosis, rather than after failure of nonpharmacological means as suggested by the ATP-II report. This prompted a recent statement from the American Heart Association Task Force on Risk Reduction that "withholding drug therapy in an effort to reach target LDL with the nonpharmaceutical approach is not necessary" in CHD patients whose LDL-C levels are more than 3.37 mmol/L (130 mg/dL).¹⁴

The ATP-II recommendations for primary prevention are particularly cautious, again based on lack of total mortality benefit seen in this population. Since that time, however, multiple primary prevention studies have demonstrated a relative risk reduction in CHD events in men treated with cholesterol-lowering therapy.¹⁵ In a sample of high-risk men from the West of Scotland Coronary Prevention Study (WOSCOPS) with mean LDL-C levels of 4.97 mmol/L (192 mg/dL), there was a 22% relative and a 0.9% absolute risk reduction in total mortality in association with a 33% relative and a 0.6% absolute reduction in coronary mortality.¹⁶ Most recently, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) demonstrated that lovastatin treatment produced a reduction in CHD events in a lower-risk population than that studied in WOSCOPS trial. Only 17% of the study cohort would have qualified for drug therapy according to ATP-II guidelines. Furthermore, treatment with statins did not appear to be associated with adverse noncoronary events.¹⁷ Given that there is significant relative risk reduction in CHD event rates possible with lipid lowering among populations with varying CHD risk, primary prevention guidelines need to consider the absolute event reduction and, as a result, the cost-efficiency of drug therapy.

The target LDL-C levels in the ATP-II report were made with data from angiographic trials and observational studies comparing LDL-C levels and CHD

mortality. Since the recommendations were made, several relevant clinical trials and post hoc analyses have been published that indirectly address the issue of optimal LDL-C treatment. The Post Coronary Bypass Graft Trial assessed surrogate end points in approximately 1350 patients who had undergone bypass grafting in the previous 1 to 11 years.¹⁸ Patients were randomized to an aggressive (ie, NCEP standard) target LDL-C level of 2.59 mmol/L (100 mg/dL) or less vs a moderate LDL-C level of approximately 3.50 mmol/L (135 mg/dL) using lovastatin, with cholestyramine added as necessary. Fewer patients showed angiographic progression and required subsequent bypass surgery with the aggressive compared with the moderate lowering approach. In the 4S trial, post hoc review suggested that both lower posttreatment LDL-C levels and greater changes in LDL-C levels from baseline were highly correlated with reduction in major coronary events.¹⁹ In the Atorvastatin Versus Revascularization Trial (AVERT), patients with mild angina were randomized to receive high-dose atorvastatin vs coronary angioplasty and/or usual medical care. The 36% relative and 8% absolute risk reduction in ischemic events in the atorvastatin group trended toward statistical significance and was associated with an LDL-C level of 1.99 mmol/L (77 mg/dL) compared with 2.08 mmol/L (119 mg/dL) in the angioplasty/usual care group. The results were limited by the small trial size ($n = 341$), the necessity for open-label design, and the heterogeneity of lipid treatment in the angioplasty/usual care group (71% were taking statins at the end of the trial).²⁰

Post hoc analysis of the results from the CARE trial suggest that no additional event-reduction benefit was achieved with pravastatin in LDL-C reduction to less than 3.24 mmol/L (125 mg/dL) compared with patients whose LDL-C levels were greater.²¹ In contrast, a treatment LDL-C threshold was not observed with simvastatin in post hoc analysis of the 4S trial.^{19(p1358)} However, post hoc analyses can often be mis-

leading; thus, this issue remains unsettled and, to date, no trials have been published comparing mortality using different LDL-C treatment targets.

For patients who have a CHD event and whose LDL-C level is already less than 2.59 mmol/L (100 mg/dL), there were no additional lipid recommendations provided in the ATP-II report. A number of trials examining the effects of aggressive LDL-C reduction beyond this level are under way, which should help provide guidance for such patients. Until these data are available, the possible approaches to such patients include increasing LDL-C reduction with statins; addition of niacin, fibric acid derivative, or bile acid resin; or a combination of these approaches. Given no current data on this subject, the practicing physician is compelled to assess further cholesterol reduction in the context of other concomitant risk factors.

Populations at Risk

Low HDL-C. The ATP-II report identified low high-density lipoprotein cholesterol (HDL-C) (<0.91 mmol/L [35 mg/dL]) as a major risk factor for CHD while recognizing high HDL-C (>1.55 mmol/L [60 mg/dL]) as protective. The report recommended that "therapeutic decisions should take into account HDL cholesterol levels." Further, HDL-C levels of less than 0.91 mmol/L (35 mg/dL) have been shown to predict increased coronary mortality in men regardless of total cholesterol level.²² A 2% reduction in CHD events in the LRC-CPPT trial was attributable to the HDL-C-raising effects of cholestyramine in addition to its LDL-C-lowering effects.^{23(p37)} Little prospective evidence of the treatment of low HDL-C is available from either primary or secondary prevention trials. In the 4S²³ and LIPID^{12(p1354)} secondary prevention trials, statin treatment reduced risk of coronary death independent of HDL-C concentration. The VA-HDL Intervention Trial (VA-HIT), examining CHD patients with both low HDL-C (<1.03 mmol/L [40 mg/dL]) and relatively low LDL-C (<3.63 mmol/L [140 mg/dL]) levels, showed a 20% relative risk reduction in CHD death and nonfatal MI with

gemfibrozil vs placebo.²⁴ The AFCAPS/TexCAPS study showed CHD event reduction using lovastatin in a primary prevention population with low to normal HDL-C (mean, 0.94 mmol/L [36 mg/dL]) and slightly elevated LDL-C (mean, 3.89 mmol/L [150 mg/dL]) levels, although the absolute benefit was small due to low event rates in both groups. Benefit with lovastatin therapy was seen only in patients whose baseline HDL-C levels were in the lowest tertiles (ie, <1.03 mmol/L [40 mg/dL]).^{17(p1621)}

Because statins have established superior benefit in the CHD population, they should be used as first-line therapy in most secondary prevention patients. Fibrates may be an acceptable alternative if the LDL-C level is less than 3.63 mmol/L (140 mg/dL) and the HDL-C level is less than 1.03 mmol/L (40 mg/dL), as suggested by the VA-HIT trial. Comparative studies of statins and fibrates in the CHD population with low HDL-C levels are not available. There are also insufficient data to specify the most appropriate means to improve risk associated with isolated low HDL-C in a primary prevention population already at LDL-C treatment goals. Given little prospective trial data, the nonpharmacological methods suggested by the ATP-II report—physical activity, smoking cessation, and weight reduction—should remain first-line therapy. Of the medical therapies, niacin achieves the greatest HDL-C improvement in the usual dosage ranges, followed by estrogen replacement therapy for postmenopausal women, fibrates, and statins. No evidence-based conclusion can be made regarding treatment of patients with isolated low HDL-C.

Young Adults. Asymptomatic atherosclerosis was demonstrated in autopsies of persons aged 2 to 39 years who died of various causes in the Bogalusa Heart Study.²⁵ The presence of cardiovascular disease correlated with antemortem ATP-II risk factors, including high LDL-C and triglyceride levels, low HDL-C level, smoking, and hypertension.²⁶ The ATP-II report suggested deferring medical therapy for hyperlipid-

emia in young adults and lowering cholesterol levels through diet and exercise in most men younger than 35 years and most premenopausal women. The report did suggest drug therapy in patients with extremely high LDL-C (>5.69 mmol/L [220 mg/dL]) or multiple CHD risk factors, usually with residuals in very young patients. Since that time, there has been suggestion by some, including the American College of Physicians, that young patients should not be screened at all, based on concern regarding the effects and expense of lifelong therapy in this population.²⁷ Since no randomized prospective trials have assessed long-term lipid-lowering therapy in this age group, no evidence-based recommendation can be made. However, the ATP-II recommendation to begin screening at age 20 years allows for more modest interventions, such as diet and weight loss, to be used in some individuals and also allows for earlier identification of familial hypercholesterolemia (FH).

Familial Hypercholesterolemia. This disorder, affecting approximately 1 in 500 persons in its heterozygous form (HeFH) and approximately 1 in 1 million persons in its homozygous form, is strongly associated with premature CHD and other vascular events.²⁸ Most authorities recommend treatment of homozygotes at diagnosis. Some have argued for initiating medical therapy for patients with HeFH beginning in childhood as well, given the tendency of these individuals to experience CHD events beginning in the third decade of life.²⁹ Recently, Stein et al³⁰ reported that treatment with lovastatin for 1 year was effective in lowering LDL-C without apparent effect on sexual maturation in boys aged 10 to 17 years old with HeFH, although the study was underpowered to detect significant safety differences.

High Cholesterol Levels in Women. The ATP-II report suggested to physicians treating hypercholesterolemia in premenopausal women to use a "cautious approach," concentrating on nonpharmacological means to reduce lipid-associated CHD risk. For female patients for whom drug therapy was recom-

mended, those with high LDL-C levels and/or multiple risk factors, estrogen was considered first-line therapy. This was likely in part due to evidence such as the apparent protective effect of estrogen replacement therapy in the Nurses' Health Study and other observational studies. In the Nurses' Health Study, there was a significant reduction in the likelihood of a major CHD event in patients who had ever taken any form of estrogen replacement.³¹ In patients with CHD, the ATP-II report suggested that "the epidemiologic evidence [was] particularly strong for secondary prevention in women with prior CHD," thus providing the basis for the recommendation of estrogen as first-line therapy in this population. Recently published results of the randomized placebo-controlled Heart and Estrogen/Progestin Replacement Study (HERS) argue against this recommendation. This study found no benefit in postmenopausal women who had had an MI and, in fact, found a 58% increase in CHD events in the first year following MI in patients treated with an estrogen/progestin combination. Lower event rates in the latter part of the 4.1-year study led to a net neutral effect of estrogen replacement therapy on rates of total mortality, CHD mortality, MI, and stroke.³² No clinical trial evidence regarding benefit of estrogen replacement in postmenopausal women without CHD is currently available.

In contrast with estrogen replacement therapy, women appear to benefit from statin therapy similar to men, although there were fewer women in the large clinical trials of these agents. Simvastatin treatment in the 4S trial was associated with a decreased coronary event rate in women, who composed less than 15% of the study sample.^{11(pp1383-1386)} In the CARE study, the relative risk reduction for major coronary events appeared even greater for women (43%) than for men (21%) with pravastatin treatment; this was despite similar lipoprotein values in both sexes.^{33(pp143)} In the LIPID trial, women achieved an 11% relative risk reduction in CHD events with pravastatin compared with a 26% reduction in the male study participants.^{12(pp1394)} Given

these data, the ATP-II recommendation to use hormone replacement therapy as first-line therapy in women with CHD is not supported. A statin should be the first-choice lipid-lowering medication in virtually all female patients with CHD. No evidence-based assessment is offered regarding ATP-II recommendations for primary CHD prevention in the premenopausal female population, given the current paucity of relevant data.

Elderly Persons. Nearly 85% of people who die from CHD are aged 65 years or older.³⁴ The increased CHD mortality in elderly persons makes lipid-lowering therapy aimed at reducing coronary events particularly attractive. Nonetheless, the ATP-II report suggested "caution in proceeding to drug therapy in the elderly" in primary CHD prevention because of increased potential for adverse medication effects. In secondary prevention, without supporting trial data, the report suggested treatment of CHD in the elderly "in the context of patients' overall health status and likelihood of benefit."

Likely because of their significantly higher baseline coronary event risk, patients older than 65 years in both the CARE and 4S trials had greater absolute coronary event risk reductions than younger patients.^{35(pp6831,36(pp4215))} In the LIPID trial, reduction in events appeared to be greatest in patients younger than 55 years, but there was event reduction in all age groups. Because none of these trials enrolled any patients older than 75 years (reaching a maximum age of 81 years by the end of the trials), no definitive conclusion regarding efficacy can be made in very elderly persons. However, currently available studies suggest lipid-lowering therapy in treatment of CHD is likely to benefit elderly patients to a similar if not greater extent than younger patients. In the area of primary CHD prevention, there is insufficient evidence to provide a recommendation beyond the ATP-II guidelines for elderly patients.

Hypertriglyceridemia. Epidemiological studies assessing hypertriglyceridemia as an independent risk factor for CHD events conflict and are confounded by its association with low

HDL-C level, hypertension, diabetes, and obesity. In addition, hypertriglyceridemia appears to be synergistic with other well-defined CHD risk factors, such as elevated LDL-C and/or low HDL-C levels, and is associated with other possible markers of atherosclerotic risk, such as small, dense LDL.³⁷ Unfortunately, no trials have specifically assessed the effects or optimal means of triglyceride lowering among patients with severe hypertriglyceridemia. This may also be a difficult population to study given its heterogeneity; however, this is an area in great need of further trial data.³⁸

Severe Forms of Hypercholesterolemia. The ATP-II report recognized the particular risk associated with FH, familial combined hyperlipidemia, and severe polygenic hypercholesterolemia. Even with the availability of high-potency statins, many of these patients require multiple forms of hypolipidemic therapy in combination. In rare circumstances, when this does not achieve an LDL-C goal, patients can undergo LDL-C apheresis, which has been associated with decreased CHD event rate and improved endothelial vasomotion.³⁹ Despite the challenges associated with treating these patients, use of multiple therapeutic modalities is justified, given the marked increase in CHD event risk seen in this population.

Transplant Recipients. A number of treatment options for immunosuppressant-induced hyperlipidemia are available, including statins and fish oils.⁴⁰ Following heart transplantation, beneficial lipid effects, decreased graft vascular disease, and improved overall survival have been achieved by using either simvastatin⁴¹ or pravastatin.⁴² Simvastatin also has been successfully used in combination with apheresis in preventing graft vessel disease in heart transplant recipients.⁴³ Another study also showed improvement in ejection fraction in heart transplant recipients treated with simvastatin; this effect appeared to be independent of lipid effects.⁴⁴ In rats, pravastatin was found to improve survival in orthotopic liver transplant recipients,⁴⁵ and in humans, to reduce

acute rejection following cadaveric renal transplantation.⁴⁶ The mechanism(s) of improved patient and graft survival in transplant recipients treated with statins may include an immunosuppressant effect(s), as episodes of severe cardiac rejection were decreased in patients treated with pravastatin compared with placebo.^{42,47} The combination of statins with cyclosporine in the transplantation setting justifies caution because cyclosporine increases potential for myopathy from statins, and statins have variable potential to increase serum cyclosporine levels.

Secondary Dyslipidemias

The ATP-II report acknowledged the high rate of CHD events in type 2 diabetes, as well as recommendations that the treatment goals in this population should be the same as for patients with established CHD. However, lacking clinical trial data, the panel suggested that type 2 diabetes in patients without known vascular disease be considered only as an additional CHD risk factor. For treatment, the panel suggested bile acid sequestrants or statins, perhaps in combination with fibric acids.

Since the ATP-II report, it has become clear that patients with type 2 diabetes without history of MI have comparable risk of MI as nondiabetic patients with history of MI. Furthermore, the 7-year risk of recurrent MI in the diabetic population was 45%, approximately 2.5 times the rate in the nondiabetic population.⁴⁸ Statin therapy was at least as effective in reducing CHD events in diabetic populations in several recent trials. As a result of these data, the American Diabetes Association (ADA) clinical practice recommendations for 1999 recommend that hypolipidemic therapy be initiated in all patients with type 2 diabetes and LDL-C levels greater than 2.59 mmol/L (130 mg/dL). The ADA-recommended treatment goal is less than 2.59 mmol/L (100 mg/dL).^{49(p559)}

Relationship Between Cholesterol and Stroke

At the time of the ATP-II report, a relationship between cholesterol and total

stroke incidence was not evident. Although the Multiple Risk Factor Intervention Trial data suggest a direct relationship between total cholesterol concentration and risk of ischemic stroke, there was an inverse association between total cholesterol levels and risk of hemorrhagic stroke; thus, the effects of lipid-lowering on overall stroke rate were not known.⁵⁰ Furthermore, no reduction in the risk of stroke from cholesterol reduction was seen in meta-analysis of either dietary or drug trials in the treatment or prevention of CHD prior to the advent of statins.^{51(p54)} Several trials did show regression of carotid intima/media thickness with statin treatment.⁵²⁻⁵⁶ Furthermore, there appears to be considerable reduction of stroke incidence in CHD patients as well. Relative reduction in stroke risk by 19% to 32% was associated with statin treatment in the CARE, 4S, and LIPID studies, as well as in meta-analyses of statin monotherapy trials by Crouse et al,^{57,58} Blauw et al,⁵⁹ and Hebert et al.⁹ Although there was a trend toward stroke reduction in primary CHD trials, the risk reduction reached statistical significance only in the secondary prevention trials. The reduction in stroke risk by statins in CHD is another rationale for their recommendation for treatment of virtually all CHD patients.

Emerging CHD Risk Factors

Since the ATP-II report, a variety of non-traditional CHD risk factors have been suggested, including measurements of inflammation, possible infection, abnormalities in vitamin B₁₂ and/or folate metabolism, abnormalities of thrombosis and/or fibrinolysis, and endothelial dysfunction.⁶⁰ In addition, more attention has been placed on the density and distribution of LDL-C particle types and HDL-C subfractions. While many of these risk factors have epidemiological associations with subsequent CHD events, no prospective randomized trials have evaluated targeting these risk factors; thus, it is not yet appropriate to formally recommend their use in a treatment algorithm.

It is consistent with the ATP-II report to treat asymptomatic patients who are

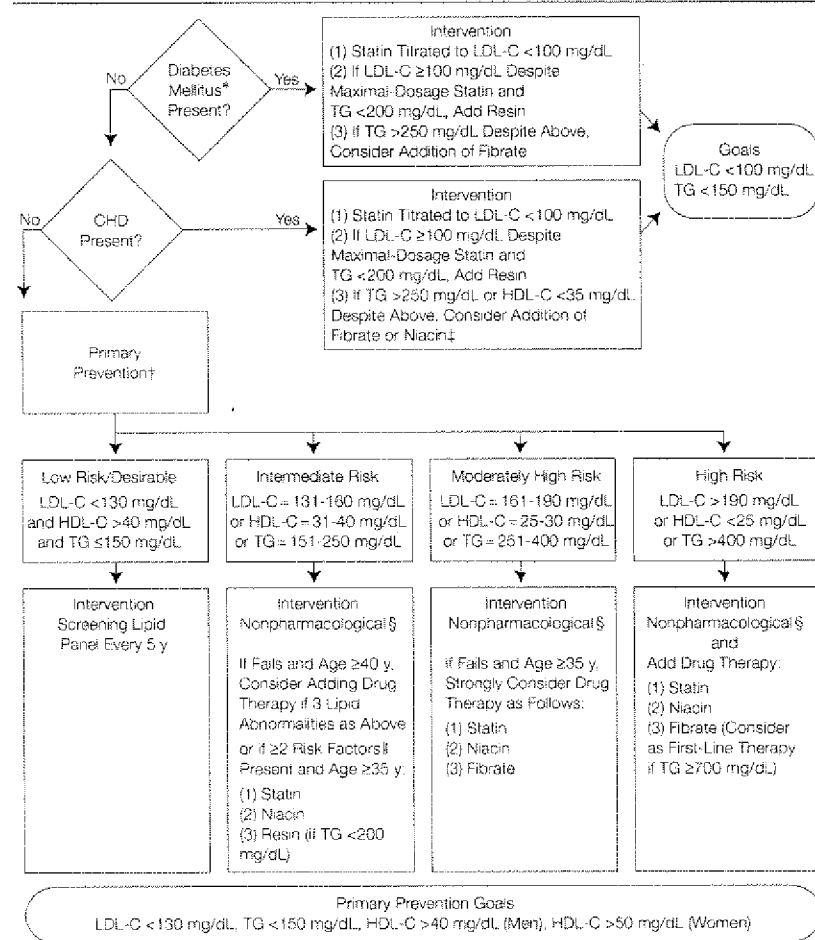
identified as having any form of atherosclerosis to a goal LDL-C level of less than 2.59 mmol/L (100 mg/dL), even though these patients have not had a CHD event. Since up to half of patients who have an MI never had angina prior to the event, using symptoms to predict risk is not justified. Patients identified with atherosclerosis are at high risk for CHD events and thus justify an aggressive approach to cholesterol lowering.

Clinical Management

From multiple lipid-lowering trials, it is clear that lowering LDL-C levels in CHD or high-risk primary prevention patients leads to clinical benefits. Still, there are not yet prospective trial data on other populations that may also be at risk due to low HDL-C or high triglyceride levels. This makes construction of an entirely trial-based treatment algorithm currently impossible. As noted,

several guidelines from other countries use estimated CHD event risk from the Framingham model to stratify necessity for treatment. In addition, variation between treatment thresholds worldwide in part reflects differing views regarding cost-effectiveness of therapy. The algorithm in the FIGURE reflects relevant findings from lipid intervention trials while emphasizing the need for global risk assessment to guide use of lipid-lowering therapy. In this treatment algorithm, lipid-lowering medication is not recommended for women of childbearing age unless known to have CHD, diabetes, or a high-risk profile for CHD as outlined. In general, medical therapy is discouraged in all primary prevention patients who are younger than 40 years who are not at "moderately high risk" (acceptable to use medication beginning at age 35 years) or "high risk" (medication may be considered after puberty).

Figure. Adult Treatment Algorithm for Preference of Lipid-Lowering Therapy Based on Findings From Lipid Intervention Trials



LDL-C indicates low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease; asterisk, type 2 diabetes of any duration or type 1 diabetes of more than 10 years' duration; dagger, lipid-lowering medication is not recommended for women of childbearing age unless the patient has known CHD or diabetes or is at high risk as described herein; double dagger, combination is not approved by the US FDA; section mark, nonpharmacological therapy includes American Heart Association diet, achieving desirable weight, and regular exercise; parallel mark, other risk factors include male sex, postmenopausal female sex, smoking, hypertension, and family history of premature CHD. To convert LDL-C and HDL-C from milligrams per deciliter to millimoles per liter, multiply by 0.02586. To convert triglycerides from milligrams per deciliter to millimoles per liter, multiply by 0.01129.

Summary

While the evidence since the publication of the ATP-II report has, to some extent, allowed for modification of some of the recommendations, the substance of the guidelines remains. Sadly, recent data suggest that as many as 25% of the adult population has not had their cholesterol measured, and the majority of patients with CHD are not treated to goal LDL-C levels. Clearly, implementation of these guidelines is as important as refining them with the most current evidence.

Recent studies demonstrate that statins benefit virtually all CHD patients and high-risk primary prevention patients, as well as confer stroke reduction benefit in CHD patients. Fibrates offer potential in reduction of triglyceride levels and small, dense LDL, and improvement of HDL-C levels, especially in CHD patients, although previous evidence of increased noncoronary mortality with this class justifies further study. The role of hormone replacement in secondary CHD prevention needs further study, but cannot be considered first-line therapy at this time. Niacin and/or resin treatment remain second-line therapies in CHD treatment and prevention, although their roles in primary low HDL-C syn-

dromes remain to be elucidated. More studies are needed to address the effects of lipid modification in women, elderly persons, and very young persons. In addition, further studies of alternate markers of lipid metabolism and risk assessment may provide alternate treatment strategies in the future.

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